Investigating the neural substrates of gambling disorder using multiple neuromodulation and neuroimaging approaches

Thèse

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Résumé

Introduction : Le trouble du jeu de hasard et d'argent (GD) est caractérisé par un comportement de jeu inadapté qui interfère avec les activités personnelles ou professionnelles. Ce trouble psychiatrique est difficile à traiter avec les thérapies actuelles et les rechutes sont fréquentes. Les symptômes dépressifs et cognitifs (e.g., l'impulsivité), ainsi que le « craving » (désir intense de jouer) sont des facteurs prédictifs de rechutes. Une meilleure compréhension des substrats neuronaux et leurs significations cliniques pourraient mener au développement de nouveaux traitements. La stimulation transcrânienne à courant direct (tDCS) pourrait être l'un de ceux-ci car elle permet de cibler des circuits neuronaux spécifiques. De plus, la tDCS ciblant le cortex dorsolatéral préfrontal (DLPFC) pourrait améliorer les symptômes dépressifs et cognitifs et réduire le craving. Cependant, les effets précis de la tDCS sur la fonction cérébrale, ainsi que leurs significations cliniques, demeurent à être élucidés. Par ailleurs, étant donné que les patients avec GD présentent souvent des différences morphométriques par rapport aux individus en santé, il est possible de faire l'hypothèse que la morphométrie cérébrale influence les effets de la tDCS.

Objectifs : Ce travail avait trois objectifs principaux. Le premier objectif était d'explorer s'il y avait des associations entre les substrats neuronaux et les symptômes cliniques et cognitifs. Le deuxième objectif était d'examiner les effets de la tDCS sur la fonction cérébrale. Le troisième objectif était d'explorer si la morphométrie du site de stimulation (DLPFC) pouvait influencer les effets de la tDCS sur les substrats neuronaux.

Méthode : Nous avons réalisé quatre études différentes. Dans la première étude, nous avons mesuré la morphométrie cérébrale en utilisant l'imagerie par résonance magnétique (IRM) structurelle. Nous avons mesuré les corrélations entre la morphométrie et les symptômes cliniques (dépression, sévérité et durée du GD) et cognitifs (impulsivité). De plus, nous avons comparé la morphométrie des patients à celui d'une base de données normative (individus en santé) en contrôlant pour

plusieurs facteurs comme l'âge. Dans la deuxième étude, nous avons mesuré la fonction cérébrale (connectivité fonctionnelle) des patients avec l'IRM fonctionnelle. Nous avons examiné s'il y avait des liens entre la connectivité fonctionnelle et les symptômes cognitifs (impulsivité et prise de risque) et cliniques (sévérité et durée du GD). Dans la troisième étude, nous avons étudié les effets de la tDCS sur la connectivité fonctionnelle et si la morphométrie du DLPFC pouvait influencer ces effets. Dernièrement, dans la quatrième étude, nous avons examiné si la morphométrie du DLPFC pouvait influencer les effets de la tDCS sur la neurochimie (avec la spectroscopie par résonance magnétique).

Résultats : Nous avons démontré deux corrélations positives entre la superficie du cortex occipital et les symptômes dépressifs (étude I). Nous avons également mis en évidence une corrélation positive entre la connectivité fonctionnelle d'un réseau occipital et l'impulsivité (étude II). De plus, il y avait une corrélation positive entre la connectivité fonctionnelle de ce réseau et la sévérité du GD. Par ailleurs, il y avait des corrélations positives entre la connectivité fonctionnelle de l'opercule frontal droit et la prise de risque (étude II). En outre, la connectivité fonctionnelle d'un réseau cérébelleux était corrélée avec les symptômes dépressifs (étude II). Les patients avaient aussi plusieurs différences morphométriques par rapport aux individus en santé (cortex occipital, préfrontal, etc.). Nous avons démontré également que la tDCS appliquée sur le DLPFC a augmenté la connectivité fonctionnelle d'un réseau fronto-pariétal (étude III). Finalement, cette thèse a montré que la morphométrie du DLPFC influence les augmentations induites par la tDCS sur la connectivité fonctionnelle du réseau fronto-pariétal (étude III) et le niveau de GABA frontal (étude IV).

Conclusions : Cette thèse démontre une importance clinique potentielle pour les régions occipitales, frontales et cérébelleuses, particulièrement pour les patients ayant des symptômes dépressifs ou cognitifs. De plus, elle montre que la tDCS peut renforcer le fonctionnement d'un réseau fronto-pariétal connu pour son rôle dans les fonctions exécutives. Il reste à déterminer si un plus grand nombre de sessions

pourrait apporter des bénéfices cliniques additionnels afin d'aider les patients à résister le jeu. Finalement, les résultats de cette thèse suggèrent que la morphométrie des régions sous les électrodes pourrait aider à identifier les meilleurs candidats pour la tDCS et pourrait être considéré pour la sélection des cibles de stimulation.

Abstract

Introduction: Gambling disorder (GD) is characterised by maladaptive gambling behaviour that interferes with personal or professional activities. This psychiatric disorder is difficult to treat with currently available treatments and relapse rates are high. Several factors can predict relapse, including depressive and cognitive (e.g., impulsivity, risk taking) symptoms, in addition to craving (strong desire to gamble). A better understanding of neural substrates and their clinical significance could help develop new treatments. Transcranial direct current stimulation (tDCS) might be one of these since it can target specific neural circuits. In addition, tDCS targeting the dorsolateral prefrontal cortex (DLPFC) could improve depressive and cognitive symptoms as well as reduce craving. However, the precise effects of tDCS on brain function, as well as their clinical significance, remain to be elucidated. Furthermore, considering that patients with GD often display morphometric differences as compared to healthy individuals, it may be worth investigating whether brain morphometry influences the effects of tDCS.

Objectives: This work had three main objectives. The first objective was to explore whether there were associations between neural substrates and clinical and cognitive symptoms. The second objective was to examine the effects of tDCS on brain function. The third objective was to explore whether morphometry of the stimulation site (DLPFC) influenced the effects of tDCS on neural substrates.

Methods: We carried out four different studies. In the first study, we investigated brain morphometry using structural magnetic resonance imaging (MRI). We tested for correlations between morphometry and clinical symptoms (depression, GD severity, GD duration) and cognitive symptoms (impulsivity). In addition, we compared the morphometry of patients with GD to that of a normative database (healthy individuals) while controlling for several factors such as age. In a second study, we assessed brain function (functional connectivity) in patients with functional MRI (fMRI). We examined whether there were associations between brain function and cognitive symptoms (impulsivity and risk taking) as well as clinical symptoms (GD severity and duration). In the third study, we examined tDCS-induced effects on

brain function and whether morphometry of the DLPFC influenced these effects. Lastly, in the fourth study, we examined whether DLPFC morphometry influenced tDCS-induced effects on neurochemistry (using magnetic resonance spectroscopy imaging).

Results: Firstly, we found two positive correlations between surface area of the occipital cortex and depressive symptoms (study I). We also showed a positive correlation between functional connectivity of an occipital network and impulsivity (study II). In addition, there was a positive correlation between functional connectivity of this network and GD severity (study II). In addition, there were positive correlations between functional connectivity of the right frontal operculum and risk-taking (study II). Also, functional connectivity of a cerebellar network was positively correlated with depressive symptoms (study II). Moreover, patients with GD had several morphometric differences as compared to healthy individuals (occipital and prefrontal cortices, etc.). Furthermore, we observed that tDCS over the DLPFC increased functional connectivity of a fronto-parietal circuit during stimulation (study III). Lastly, this thesis indicated that DLPFC morphometry influenced tDCS-induced elevations on fronto-parietal functional connectivity (study III) and frontal GABA levels (study IV).

Conclusions: This thesis suggests the potential clinical relevance of occipital, frontal, and cerebellar regions, particularly for those with depressive and cognitive symptoms. It also indicates that tDCS can strengthen the functioning of a fronto-parietal network known to be implicated in executive functions. It remains to be seen whether a greater number of tDCS sessions could lead to clinical benefits to help patients resist gambling. Finally, the results of this thesis suggest that morphometry of the regions under the electrodes might help predict better candidates for tDCS and could be considered to select stimulation targets.

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ANOVA	Analysis of Variance
BART	Balloon Analog Risk Task
BDI	Beck Depression Inventory
BIS	Barratt Impulsiveness Scale
BOLD	Blood oxygen level dependent
cTBS	Continuous theta burst stimulation
DLPFC	Dorsolateral prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th ed.)
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GD	Gambling Disorder
Glx	Glutamine + glutamate
ICA	Independent component analysis
IFG	Inferior frontal gyrus
iTBS	Intermittent theta burst stimulation
MDD	Major Depressive Disorder
MRI	Magnetic resonance imaging

MRSI	Magnetic resonance spectroscopy imaging
NMDA	N-methyl-D-aspartate
OCD	Obsessive Compulsive Disorder
PFC	Prefrontal cortex
PET	Positron emission tomography
ROI	Region of interest
Rs-FC	Resting state functional connectivity
RCT	Randomized controlled trial
rTMS	Repetitive transcranial magnetic stimulation
SOGS	South Oaks Gambling Screen
SRAD	Substance-Related and Addictive Disorder
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance Use Disorder
tDCS	Transcranial direct current stimulation

To my loving parents - Leslie and Jean-Pierre

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Be bold, be bold, and everywhere be bold - Herbert Spencer

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Preface

This thesis examines the neural substrates of Gambling Disorder using transcranial direct current stimulation and neuroimaging techniques such as fMRI, structural MRI and MRSI. Results of this thesis are presented in Chapters 2, 3, 4, and 5. In all four studies, I led the data analyses and interpretation of results, as well as drafting and reviewing the manuscripts. Each study is based on the same sample of patients with Gambling Disorder who met DSM-5 diagnostic criteria for GD (F. Ferland). M. Dickler and F. Ferland recruited the patients. It should be noted that the morphometry and fMRI data in chapters 2 and 3 represent the first and second baseline (pre-tDCS) sessions of the tDCS-fMRI study (Chapter 4), respectively. This was a randomized, sham-controlled crossover study (both tDCS sessions were provided at least 7 days apart). Hence, there were no potential influences of tDCS on these measures.

A version of Chapter 2 was published in *Journal of Psychiatry Research*:
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The manuscript for Chapter 3 is under preparation:
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A version of Chapter 4 was published in *Brain Connectivity*:
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The study in Chapter 5 was published in *Brain Stimulation*:
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tDCS effects on GABA levels. Brain Stimul **13**(2): 284-286. Doi: 10.1016/j.brs.2019.10.013.

Lastly, this thesis includes a book chapter that was written during my PhD studies and was published by Springer. I was responsible for reviewing the literature as well as writing the first draft of the book chapter. It is presented in Appendix I:

Bouchard, A. E., S. Garofalo, C. Rouillard and S. Fecteau (2021). Cognitive Functions in Substance-Related and Addictive Disorders. Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management. A. R. Brunoni, M. A. Nitsche and C. K. Loo. Cham, Springer International Publishing**:** 519-531. doi: 10.1007/978-3-030-76136-3_26.

Introduction

1.1 Gambling Disorder

A substance-related and addictive disorder (SRAD) is a psychiatric disorder that is illustrated by a repetitive behaviour that activates the reward system (American Psychiatric Association 2013). SRADs include substance use disorders (SUDs), where individuals misuse substances (alcohol, cannabis, cocaine, tobacco, etc.). Emerging evidence also suggests the inclusion of non-substance-related disorders, which share characteristics with SUDs, such as Gambling Disorder (GD). Gambling is defined as risking something of value while hoping to gain something of larger value (Potenza et al. 2001). It is believed that gambling has taken place since the dawn of civilization, where, 7000 years ago, Mesopotamians gambled using astragali (Schwartz 2013) (see **Figure 1**).

Figure 1. **Astragali**. The astragalus is the ancient ancestor of modern dice and is made of animal bones (e.g., sheep). Each side is thought to represent a different number, similarly to present-day dice (in green and red). *Reproduced from Karnavalfoto/Shutterstock.com*

Today, most adults gamble (Welte et al. 2015). Indeed, 80-85% of Canadians and Americans have gambled at least once in their lifetime and nearly 2 out of 3 of Americans have gambled in the past year (Auter 2016). Popular gambling activities

include casino gambling (e.g., slot machines), lotteries, and online gambling (e.g., poker) (Potenza et al. 2019). Yet, for a subset of individuals, gambling is pathological, that is, it significantly interferes with their personal, familial, or occupational lives.

According to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), pathological gambling is defined as a "persistent and recurrent maladaptive gambling behavior" (American Psychiatric Association 1994). In the DSM-5, "Pathological gambling" was replaced with GD (American Psychiatric Association 2013). Previously classified as an "Impulse-Control Disorder Not Elsewhere Classified" in the 4th edition, it was added to the SRADs section in the 5th edition largely in part to help clarify its diagnosis and treatment (Petry et al. 2013), as well as to show its similarities to SUDs (Grant et al. 2010a) (see **Box 1** for GD diagnostic criteria).

GD is a debilitating disorder that affects both patients and their close ones (Petry et al. 2013, Potenza et al. 2019). For example, patients with GD can display serious consequences, including bankruptcy, relationship problems and even suicide (i.e., 15-fold higher suicide rates than average, (Karlsson and Håkansson 2018, Potenza et al. 2019)). In addition, GD is linked to poor physical health (Hong et al. 2009; Germain et al. 2011; Black et al. 2013; Potenza et al. 2019). For instance, GD severity is positively correlated with the number of medical ailments (Black et al. 2013). Patients with GD can experience high stress level (e.g., when losing money), as well as a sedentary lifestyle that can promote medical related conditions such as obesity (Black et al. 2013; Butler et al. 2019), all of which can contribute to heart disease (Black et al. 2013). Understandably, patients and their loved ones can have a low quality of life (Potenza et al. 2019).

Likewise, GD and SUDs share many characteristics, including behaviours, heritability, cognitive deficits (Petry et al. 2014; Rash et al. 2016). Additionally, a large proportion of patients with GD display psychiatric comorbidities including SUDs

Box 1. DSM-5 diagnostic criteria for 312.31 (F63.0) Gambling Disorder

A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

B. The gambling behavior is not better explained by a manic episode.

Specify if:
Episodic: Meeting diagnostic criteria at more than one time point, with symptoms subsiding between periods of gambling disorder for at least several months.
Persistent: Experiencing continuous symptoms, to meet diagnostic criteria for multiple years.

Specify if:
In early remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met for at least 3 months but for less than 12 months.
In sustained remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met during a period of 12 months or longer.

Specify current severity:
Mild: 4-5 criteria met.
Moderate: 6-7 criteria met.
Severe: 8-9 criteria met.

Note: Although some behavioral conditions that do not involve ingestion of substances have similarities to substance-related disorders, only one disorder—gambling disorder—has sufficient data to be included in this section.

and depression/mood disorders. The most common comorbidity is Tobacco Use Disorder, which affects about 70% of patients with GD (Kessler et al. 2008).

Furthermore, gambling opportunities are rising in countries such as Canada and the USA. For instance, there was a recent increase in legalization of state lotteries in the USA (Welte et al. 2015). Individuals are also increasingly participating in sports-related gambling events. For instance, the 2019 Kentucky Derby held a record-breaking 165.5 million USD dollars in bets (Shapiro 2019). In addition to this, there is an explosion in online gambling activities, largely due to continuous advances and availability in technology and the internet (Abbott 2017). Ultimately, these increases in legalization and activity are a public health concern (Calado and Griffiths 2016). Indeed, GD is now recognized as an understudied mental disorder (The Lancet Public Health 2021). Greater awareness efforts are thus needed to protect vulnerable individuals and prevent gambling-related negative consequences.

1.1.1 Description of symptoms

Patients with GD can display several symptoms similar to SUDs that make it difficult to quit (i.e., contribute to relapse and treatment adherence). Thus, targeting symptoms is important. These include cognitively related symptoms (e.g., impulsivity and risk-taking) and craving. Firstly, impulsivity refers to hasty, unplanned reactions to internal or external stimuli without thought to the consequences to oneself or to others (Potenza 2014). Several studies have found that patients with GD display greater impulsivity level as compared to healthy individuals (MacKillop et al. 2011; Michalczuk et al. 2011; Kraplin et al. 2014; Chowdhury et al. 2017; Limbrick-Oldfield et al. 2020). Impulsivity can also affect individuals with problem gambling (i.e., that are at risk of GD) (Ioannidis et al. 2019). As shown in a recent study, both patients and their unaffected siblings displayed higher impulsivity level compared to healthy individuals (Limbrick-Oldfield et al. 2020). Genetics might thus be a contributing factor of impulsivity.

Compulsivity represents the tendency to take part in repetitive behaviours, sometimes with perseverations (Potenza 2014). Gambling activities may start as

impulsive (e.g., gambling for reward) and become compulsive over time (e.g., habit). Also, some patients can have rituals and superstitions, such as having a lucky number or wearing a certain colour or item of clothing to increase odds of winning (Grant et al. 2016). Impulsivity and compulsivity appear particularly important to understanding GD, as suggested by a recent international Delphi consensus (Yücel et al. 2019).

In addition, risk-taking, which involves making risky choices, is higher in patients with GD as compared to healthy individuals (Lawrence et al. 2009; Grant et al. 2011a; Zois et al. 2014; Ciccharelli et al. 2016; Kovacs et al. 2017; Limbrick-Oldfield et al. 2020). Highly associated with impulsivity, risk-taking can manifest itself as the inability to resist gambling (Kovacs et al. 2017). Risk-taking might also be a vulnerability factor for GD, since elevated levels were present in patients and their unaffected siblings as compared to healthy individuals (Limbrick-Oldfield et al. 2020).

Interestingly, patients with GD can display what appear to be GD-specific symptoms akin to magical thinking and superstitions, including “chasing” one’s losses, illusions of control, and the “gambler’s fallacy” (Potenza 2014; Potenza et al. 2019). Chasing one’s losses refers to gambling to win back lost money. Also, illusions of control are beliefs that one has control over events when in reality one does not. In addition, the “gambler’s fallacy” occurs when one believes that an event will occur based on the occurrence of another independent event. For example, a patient may believe that the odds of landing a 3 during dice rolling is not 1 out of 6 when landing on a 3 several times in a row. Furthermore, patients can display a subtle form of tolerance, which occurs when they need to gamble with increasing amounts of money to reach the same amount of excitement that they previously experienced. Also, patients can display loss of control, i.e., they cannot control or stop their gambling. Moreover, patients with GD can show negative affect (irritability, depression, etc.), which can contribute to gambling (e.g., to relieve negative affect) (Jauregui et al. 2016; Rogier and Velotti 2018).

Lastly, patients with GD can display craving. Craving was recently added as a criterion in the latest version of the DSM for SUDs (American Psychiatric Association 2013). According to the DSM-5, craving is defined as an "intense desire or urge for the drug that may occur at any time but is more likely when in an environment where the drug was previously obtained or used" (American Psychiatric Association 2013). Craving is an important symptom to target since it is a strong predictor of relapse in both SUDs and GD. For instance, it can increase the chances of relapse by 29% in patients with GD (Smith et al. 2015). However, craving was added as a criterion for SUDs only, despite it also being pertinent for other SRADs, including GD. Indeed, craving is central to the pathophysiology of GD, and it has a similar circuitry as SUDs (e.g., circuits implicating the PFC and ventral striatum) (Koob and Volkow 2016; Fauth-Buhler et al. 2017; Limbrick-Oldfield et al. 2017). It is thus pertinent to suppress craving in GD to help patients decrease (and ultimately stop) gambling.

Altogether, patients with GD can display a variety of symptoms. However, it is unclear whether the symptoms are a cause and/or a consequence. Also, scientists and clinicians should consider studying and modulating gambling craving, given its importance for relapse and treatment adherence. In addition, not all patients with GD display the same symptoms and to the same extent (it an also vary within an individual depending on the course of the GD). More research is needed to further our understanding of this complex disorder. The field also merits a better understanding of the prevalence of this disorder as well, especially since many patients do not seek help (Slutske 2006).

1.1.2 Prevalence

The global prevalence rate of GD in the past 12 months is estimated to be between 0.12-5.8% (Calado and Griffiths 2016). In Canada and the USA, GD affects about 1-3% of individuals (Cox et al. 2005; Stucki and Rihs-Middel 2007). To note, prevalence differs from study to study, which is possibly due to differing screening tools (Potenza et al. 2019). In fact, according to a recent systematic review, about 90% of screening tools lacked adequate methodological quality (Otto et al. 2020). In

addition, GD is under-recognized by clinicians (Dannon et al. 2006). Considering that the diagnostic criteria for GD have changed over the years, better screening tools, as well as unanimity between the DSM and ICD, are needed to improve diagnoses.

Furthermore, in the Americas, GD is more prevalent among African Americans, Hispanics, and Indigenous peoples, as compared to Caucasians and Asians (Welte et al. 2015). Also, low income, non-married younger adults are more likely to display GD (Abbott 2017). In addition, male adolescents with comorbid psychiatric disorders and early onset of gambling activities have more chance of displaying GD, compared to other adolescents (Floros 2018). It is also estimated that GD affects twice more males than females (Welte et al. 2015). Men appear to begin gambling at younger ages than women (Grant et al. 2012; Vizcaino et al. 2014). Additionally, younger, but not older adults are more inclined to chase their losses (Sacco et al. 2011). Men seem to prefer strategic gambling activities (e.g., poker, blackjack), whereas women tend to choose nonstrategic gambling activities (e.g., electronic gaming machines) (Potenza et al. 2019). Women are also more prone to “telescoping” (i.e., faster development of gambling-related problems, although gambling activity is initiated at a later age) (Zakiniaeiz et al. 2017). In addition, women are more prone to be distressed (Hakansson and Widinghoff 2020), as well as gamble to relieve depression or to escape (Sacco et al. 2011). To note, prevalence estimates are difficult to obtain, since a small number of participants seek treatment. Treatments will be discussed next.

1.1.3 Current treatments and success rates of these treatments

It is estimated that 10% of patients with GD seek treatment (Slutske 2006). This might be due to fear of stigmatization or unawareness of treatment options (Menchon et al. 2018; Palmer et al. 2018; Quigley et al. 2019). More work is also needed in certain health systems such as Quebec to better integrate detection and treatment services. In addition, denial likely influences treatment seeking or adherence (Shah et al. 2019). Patients may seek help for several reasons, such as internal (e.g.,

negative emotions) and external (e.g., financial stress) factors (Suurvali et al. 2010). There are no approved medications for GD. The following sections will describe pharmacological, behavioural, and psychosocial treatments in GD, starting with medications.

1.1.3.1 Pharmacological treatments

Although various pharmacotherapies have been proposed to treat GD, none are currently approved to treat GD. The main medications aim to treat dysfunctional neurotransmitter systems in GD. Opioid antagonists, antidepressants and mood stabilizers are the most studied medications to treat GD (Di Nicola et al. 2019). They were suggested based on past knowledge of neural substrates, e.g., similarities with other disorders. For example, antidepressants were first studied for GD 20 years ago, when GD was categorised as an Impulse Control Disorder and serotonin is thought to play a main role in impulse control. The next sections will discuss the drugs that have been proposed to treat GD, starting with opioid antagonists.

1.1.3.1.1 Opioid antagonists

Naltrexone and nalmefene are the main opioid antagonists proposed to treat patients with GD (Piquet-Pessôa and Fontenelle 2016). They are both mu- and delta-opioid receptor antagonists that work differently on the kappa receptor. Naltrexone is an antagonist and nalmefene is a partial agonist (Swift 2013). They are both approved to treat Alcohol Use Disorder and Opioid Use Disorder. These two medications are thought to affect the opioid neurons of the arcuate nucleus, in turn influencing meso-limbic dopamine circuitry, therefore decreasing craving to help patients maintain abstinence (Piquet-Pessôa and Fontenelle 2016). Experts now believe that opioid antagonists hold the most promise to treat GD (Kraus et al. 2020).

Six studies evaluated the effects of naltrexone (Kim et al. 2001; Dannon et al. 2005; Grant et al. 2008; Toneatto et al. 2009; Lahti et al. 2010; Kovanen et al. 2016). Two RCTs reported improvements, including decreased gambling activity (Kim et al. 2001) and GD severity (Grant et al. 2008). Moreover, patients with stronger craving

had better responses (Kim et al. 2001), similar to findings in Alcohol Use Disorder (Anton 2013; Subbaraman et al. 2013). However, many of the patients reported side effects, including nausea, dry mouth, and vivid dreams (Kim et al. 2001). Two other RCTs combined naltrexone with psychotherapy, yet there were no differences as compared to placebo plus psychotherapy on alleviating symptoms such as GD severity and craving (Toneatto et al. 2009, Kovanen et al. 2016). In addition, a randomized (but not placebo-controlled) study compared the effects of 12 weeks of naltrexone than buproprion (an antidepressant, discussed in the next section) (Dannon et al. 2005). The authors found that both treatments induced similar improvements in symptoms, that is, 75% and 76% were full completers in the buproprion and naltrexone groups, respectively (completers had improvements in symptoms and stopped gambling for 2 weeks). Lastly, an open-label study found that as-needed naltrexone improved quality of life and reduced depressive symptoms, as well as obsessive-compulsive gambling behaviours (Lahti et al. 2010).

Furthermore, 2 RCTs assessed the effects of nalmefene. The first RCT compared 3 doses of nalmefene (25, 50, 100 mg/day) as compared to placebo (Grant et al. 2006). They found significant reductions in GD severity for patients who received 25 or 50mg of nalmefene than placebo. However, nalmefene was associated with many side effects such as nausea (38.5% for patients receiving 50mg of nalmefene in comparison to 7.8% in the placebo group) and insomnia (36.5% for 50mg of nalmefene as compared to 19.6% for placebo). In addition, 66% of patients dropped out before the end of the treatment period (only 47% and 31% of patients assigned to placebo and nalmefene groups completed the 16-weeks, respectively). The other RCT did not find significant differences between nalmefene and placebo on primary and secondary outcome measures (e.g., GD severity, gambling symptoms) (Grant et al. 2010b).

1.1.3.1.2 Antidepressants

Antidepressants include selective serotonin reuptake inhibitors (SSRIs) and buproprion. SSRIs are the most used and are approved for mood disorders. Five

RCTs exist on SSRIs in GD (Hollander et al. 2000; Blanco et al. 2002; Kim et al. 2002; Grant et al. 2003; Saiz-Ruiz et al. 2005). Only 40% of these studies support the use of the SSRIs (paroxetine (Kim et al. 2002) and fluvoxamine (Hollander et al. 2000)), as they reduced GD severity and craving as compared to placebo and they were well tolerated by patients. However, long-term effects were not assessed in either study. Also, all patients were male in one study (Hollander et al. 2000). Hence, the findings might not be generalizable to all patients with GD. In addition, SSRIs can cause side effects, e.g., drowsiness, nausea, and insomnia. For example, in one of these studies, patients who received fluvoxamine in one study had significantly higher nausea than those that received the placebo (medication: 41%; placebo: 12%) (Blanco et al. 2002).

Subsequently, bupropion, a dopamine and norepinephrine reuptake inhibitor, is currently approved for Tobacco Use Disorder, Major Depressive Disorder and Seasonal Affective Disorder (Patel et al. 2016). Three studies examined bupropion and found mixed results. One study observed that bupropion was as effective as naltrexone to reduce gambling symptoms (as discussed in the previous section) (Dannon et al. 2005). One double-blind RCT reported no differences between 12 weeks of bupropion or placebo on GD severity and there were high attrition rates (43.6%) (Black et al. 2007). Lastly, a more recent study investigated the effects of 12 weeks of bupropion on symptoms and brain function in patients with internet-based GD and Internet Gaming Disorder (Bae et al. 2018). Both groups of patients displayed improvements in symptoms after the treatment, including reduced impulsivity, depressive symptoms, and disorder severity. In addition, both groups displayed changes in brain function (resting state functional connectivity, discussed in a later section) that were associated with reductions in disorder severity. Interestingly, such correlations involved different circuits (a parietal network and a posterior cingulate-parietal network for GD and Internet Gambling Disorder patients, respectively), suggesting that bupropion might affect patients differently in both disorders. However, this was not a placebo-controlled study, hence it is impossible to rule out whether there was a placebo effect. In addition, bupropion can cause side

effects which can impact adherence. For instance, in one study, 5 out of 17 patients dropped out, the majority (80%) doing so due to side effects including vertigo, gastrointestinal disturbances, and/or dizziness (Dannon et al. 2005). Hence, more research, especially larger, double-blind RCTs, are needed to investigate the effects of nalmefene in GD. Other treatment options include mood stabilizers.

1.1.3.1.3 Mood stabilizers

Lithium and topiramate are the main mood stabilizers proposed to treat GD (Di Nicola et al. 2019). Firstly, lithium was proposed since it can treat Bipolar Disorder and it shares substrates with Impulse Control Disorders (McElroy et al. 1996) (as mentioned in an earlier section, GD was previously considered to be an Impulse Control Disorder). Although its mechanisms of action are not fully understood, lithium is thought to influence various processes, such as stimulating inhibitory transmission and stopping excitatory signalling (Alda 2015). One double-blind RCT assessed the effects of sustained-release lithium carbonate in patients with GD and Bipolar Disorder over 10 weeks (Hollander et al. 2005). Patients improved on several measures, e.g., GD severity and mood. Also, there was a negative correlation between improvement in mania and GD severity. Although the results are positive, they may only benefit GD patients with co-morbid bipolar disorders.

In addition, topiramate was suggested for GD as it can decrease craving (Johnson et al. 2003) and drinking (Johnson et al. 2007) in Alcohol Use Disorder. Topiramate is a GABA receptor agonist and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate glutamate receptor blocker (Berlin et al. 2013, de Brito et al. 2017) that may indirectly decrease cortico-meso-limbic dopamine release to reduce craving. One study comparing 2 medications, but not placebo-controlled, found that 12 weeks of topiramate improved symptoms (e.g., GD severity), but not fluvoxamine (Dannon et al. 2005). Two RCTs evaluated topiramate in patients with GD. The first study found that 14 weeks of topiramate did not induce significant differences on primary and secondary outcome measures as compared to placebo, including GD severity (Berlin et al. 2013). On the other hand, the second study

reported significant improvement on several measures (e.g., craving, money spent gambling, cognitive distortions, and time spent gambling) after 12 weeks of topiramate combined with 4 sessions of cognitive behavioural therapy (discussed in a later section) as compared to placebo with the same behavioural intervention (de Brito et al. 2017). Although this seems promising, it is unclear whether the improvements were due to the interaction between the 2 interventions. One suggestion for future studies is to compare 5 groups, as such: 1) topiramate only; 2) topiramate and CBT; 3) CBT only; 4) placebo only; 5) no intervention, to better understand the effects of each treatment.

Overall, it seems that mood stabilizers may not be the best treatment for GD. Further, mood stabilizers can cause side effects. For instance, topiramate can impair cognitive abilities (e.g., slowed thinking and concentration), as well as induce dizziness, paresthesia, and ataxia (Jones 1998). In addition, common side effects of lithium include frequent urination, nausea, diarrhea, tremor, and cognitive impairment, and even hypothyroidism (Gitlin 2016). Understandably, all these side effects could influence treatment adherence. There is a line of evidence for the use of other medications such as dopamine, GABA, glutamate modulators, as well as sedatives, which will be discussed next.

1.1.3.1.4 Other medications

Other medications have been considered, including acamprosate, baclofen, as well as blonanserin, olanzapine, ketamine, memantine, and n-acetyl cysteine. Firstly, acomprosate is an indirect partial N-methyl-D-aspartate (NMDA) receptor agonist and a metabotropic glutamate receptor antagonist (Mason and Heyser 2010) that is currently approved to treat Alcohol Use Disorder. One case study reported that acamprosate helped a GD patient with comorbid Alcohol Use Disorder and a history of Major Depressive Disorder quit both drinking and gambling after taking this medication for 1 month (Raj 2010). Additionally, in one open label study, an acamprosate treatment of 8 weeks was associated with clinical improvement, such as reduced GD severity and gambling activity (Black et al. 2011).

Secondly, baclofen is a dopamine inhibitor (Addolorato et al. 2009) that is used off label for treating SUDs. In an open-label study, men with GD received either baclofen or acomprosate, for 6 months with monthly follow ups (Dannon et al. 2011). Neither drug was effective at helping patients maintain abstinence during the half year period. These medications can also cause side effects such as nausea, apathy and weakness (Dannon et al. 2011). Additionally, a more recent case study found that baclofen worsened GD severity in a patient with co-morbid GD and Alcohol Use Disorder (Guillou-Landreat et al. 2017). Thirdly, blonanserin, a dopamine D3 receptor antagonist, was given during eight weeks to one patient with GD and comorbid intellectual disability and physical health issues (e.g., type I diabetes mellitus) (Shiina et al. 2021). Although the patient showed decreased impulsivity and GD severity, she stopped taking the medication due to excessive saliva production. Consequently, her symptoms worsened as compared to baseline. Thus, this treatment does not seem promising.

In addition, olanzapine, a dopamine antagonist, was proposed as a treatment for GD, mostly since it alleviated symptoms in patients with Impulse Control Disorders, such as Trichotillomania (Stewart and Nejtek 2003). As previously discussed, GD was once classified as an Impulse Control Disorder, so one could suppose that olanzapine could be a good treatment. Two RCTs did not support the use of olanzapine for GD, as it did not induce significant effects on several measures, such as craving (Fong et al. 2008) and GD severity (McElroy et al. 2008), as compared to placebo. Additionally, there was high dropout, where 52% of patients who received olanzapine and 29% that received placebo did not complete the 12-week intervention (McElroy et al. 2008). Patients discontinued the treatment due to low effectiveness, problems with adherence and side effects (sedation, hypomania, pneumonia, etc.) (McElroy et al. 2008). Also, olanzapine can increase appetite, thereby possibly causing weight gain, as well as sedation and dry mouth (Conley and Meltzer 2000), which may affect treatment adherence.

Furthermore, a case study tested intravenous ketamine, an NMDA antagonist that can decrease craving in SUDs (Jones et al. 2018), possibly by improving glutamate homeostasis in the PFC (Ma et al. 2009) in one patient with GD. After receiving 4 sessions of ketamine over 2 weeks, the patient's GD severity declined from high to low (reaching a subclinical threshold), which lasted 6 months (Grant and Chamberlain 2020). Another study assessed a different NMDA receptor antagonist called memantine. After 10 weeks of this medication, patients displayed decreased GD severity, as well as reduced hours and amounts of money spent gambling each week and improved cognitive flexibility (Grant et al. 2010). Interestingly, 97% of patients completed the study, which is exceptional, considering the common high drop-out rates usually observed in GD. Although this study has encouraging results, it would be important to conduct double-blind RCTs to make more sound conclusions.

Lastly, 2 studies examined n-acetyl cysteine. N-acetyl cysteine is an amino acid and cysteine prodrug, a compound that activates its properties after it is metabolized, that restores extracellular glutamate levels in the nucleus accumbens in preclinical models (Baker et al. 2003). It has reduced craving level and withdrawal symptoms in individuals with Cocaine Use Disorder (LaRowe et al. 2006). In one study, patients with GD received either n-acetyl cysteine or placebo in an 8-week open label phase, where responders (those that displayed sufficient decreased GD severity, that is 59% of patients) entered a subsequent six-week, double-blind, placebo-controlled phase (Grant et al. 2007). After this phase, 83% of those who received the medication remained responders as compared to 29% of those who took the placebo. Yet, there were nonsignificant improvements in symptoms such as craving. In a follow-up 12-week double-blind RCT, n-acetyl cysteine combined with psychotherapy decreased Tobacco Use Disorder severity during the first half (6 weeks) of the treatment period in patients with GD and comorbid Tobacco Use Disorder (Grant et al. 2014). Interestingly, those who received n-acetyl cysteine as compared to placebo had decreased GD severity at the 3-month follow-up.

Altogether, some medications, such as opioid antagonists and antidepressants, may be promising. However, blinded RCTs are lacking. They are needed so robust clinical conclusions can be made as to which medication (if any), is best for patients with GD. Also, there are many side effects, which can undoubtedly impair adherence. Experts in the GD field recommend combining medications with behavioural interventions to boost outcomes and patient retention (Potenza et al. 2019; Kraus et al. 2020), although more research is needed to test this out.

1.1.3.2 Psychosocial and behavioural interventions

The main objective of non-pharmacological treatments for patients with GD is to change the patients' behaviours as well as improve their cognitive control and motivation to reduce, and ultimately cease gambling (Ribeiro et al. 2021). Numerous psychosocial and behavioural interventions have been studied. The following is a review of studies that examined behavioural interventions over the last 20 years. These interventions include Cognitive Behavioural Therapy, mindfulness-based interventions, motivational interventions, imaginal desensitization, Gamblers Anonymous, self-help interventions, and couples' therapy.

1.1.3.2.1 Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is the most studied and recommended treatment for GD (Potenza et al. 2019). CBT, as its name suggests, tackles both the cognitive and behavioural aspects of gambling. The cognitive part aims to correct the patient's attitudes, beliefs and thoughts that underlie cognitive symptoms or craving (Ribeiro et al. 2021). For example, CBT can use cognitive restructuring to correct maladaptive gambling-related thoughts that contribute to GD (Chretien et al. 2017), such as cognitive distortions (e.g., inaccurate beliefs or rituals regarding collecting wins (Potenza 2014, Potenza et al. 2019)). Further, the behavioural aspect of CBT is based on the idea that gambling is a learned behaviour (e.g., classical conditioning, where winning could be a powerful conditioner that hooks gamblers (Lesieur and Custer 1984)). The behavioural component of CBT can thus serve to identify a patient's triggers and help them deal with the response to such triggers

(Sharpe and Tarrier 1993), as well as promote healthy coping strategies or alternatives to gambling (Ribeiro et al. 2021).

Overall, studies suggest that CBT may be a good option for the short-term, but not necessarily for the long-term. For instance, a systematic review showed medium and large effects 0-3 months after the treatment, but not 9-12 months post-treatment to reduce gambling symptoms (GD severity, financial loss and gambling frequency, etc.) as compared to control conditions (wait list, etc.) (Cowlishaw et al. 2012). RCTs conducted since this review support the efficacy of CBT on measures such as GD severity and craving (Myrseth et al. 2011; Bouchard et al. 2017; Casey et al. 2017), with results lasting through long-term (12-months) follow-up in one study only (Casey et al. 2017). Interestingly, this study delivered CBT using the internet, where 6 weekly sessions improved several clinical measures (e.g., reduced GD severity, craving, depression, stress, anxiety, gambling-related cognitions) as compared to a waitlist control condition (Casey et al. 2017).

Hence, it might be worth considering an online approach to treat patients with GD, which might be especially interesting for patients that are more hesitant to seeking in-person help due to shame or embarrassment, fear of stigma, etc. (which is common in these patients, as discussed in a previous section (Palmer et al. 2018, Quigley et al. 2019)). However, it should also be considered that there may be differences as compared to “traditional” face-to-face CBT. For instance, the internet-based CBT approach in this work (Casey et al. 2017) was less effective at reducing gambling-related cognitions and had a higher drop-out rate (47.7% as compared to 18.6%) than a previous in-person CBT regimen conducted by the same team (Oei et al. 2010) (they compared effect sizes across both studies). It might also be beneficial for patients to receive guidance from a therapist while undergoing self-directed online CBT, which improved clinical measures (e.g., craving) more so than online CBT without guidance in a recent RCT that compared the efficacy of both interventions (Dowling et al. 2021).

Another factor that might be worth considering is to enhance CBT with mindfulness meditation to further boost strengthening cognitive control (e.g., reducing cognitive distortions and irrational beliefs). Mindfulness meditation is metacognitive in nature, as it underscores non-judgemental awareness of mental content (Grabovac et al. 2011). In a context for GD, mindfulness meditation could be used to help patients respond to maladaptive cognitive processes with an accepting and non-judgemental mindset to help them recognize such processes and motivate them to change. There is a line of evidence that mindfulness meditation can decrease craving and substance misuse in SUDs (Garland and Howard 2018). As of date, one study reported that 5 sessions of CBT combined with mindfulness mediation improved symptoms such as GD severity and craving as compared to control (waitlist) (Toneatto et al. 2014).

Although there has been a substantial increase in studies examining the effects of CBT in GD over the years, larger RCTs are still needed to better elucidate how it should be delivered (e.g., in person, online), as well as whether effects are clinically significant. It will also be important to determine whether the effects last over the long-term (e.g., using follow-up measures) and if there is a need for maintenance CBT sessions. Another approach that might be useful is motivational therapy.

1.1.3.2.2 Motivational therapy

Motivational therapy aims to resolve ambivalence by helping patients change their behaviours regarding their gambling activity (e.g., realizing that it is problematic and wanting to change). A 2012 Cochrane review paper assessing RCTs of behavioural treatments for GD suggested that motivational therapy reduced financial losses in the short-term (0-3 months post-treatment), but there was insufficient data for other outcome measures (Cowlishaw et al. 2012). In addition, a more recent meta-analysis examining RCTs for motivational therapy (1 to 6 sessions) found significant reductions in gambling frequency (average days gambled per month) and gambling expenditure (money lost to gambling) as compared to controls (non-motivational interviewing or no treatment) post-treatment (Yakovenko et al. 2015). They also

found a significant effect of the former (but not the latter) over both the short- and long-term (up to 12 months follow-up). Although these results seem promising, it should be noted that the average decrease in gambling frequency varied from 1.3 days at immediate post-treatment to 1.12 days at long-term (up to 12 months) follow-ups, thus more research is needed to elucidate the clinical relevance.

Furthermore, two studies demonstrated that 6 sessions of motivational therapy combined with imaginal desensitization (outlined in the next section) improved symptoms such as GD severity, symptoms and/or mood as compared to the control condition (referral to Gamblers Anonymous; discussed in a subsequent section) (Grant et al. 2009; Grant et al. 2011b). In addition, patients who did not respond to Gamblers Anonymous were offered the other treatment and they demonstrated improved symptoms. Grant et al. (2011b) carried out a 6-month follow-up and found that most improvements in symptoms were maintained. However, there were worsening of some scores at the follow-up, such as GD severity, which was potentially mediated by comorbid tobacco smoking. Thus, patients with comorbid SUDs may need more tailored care to help them maintain abstinence, such as maintenance therapies.

1.1.3.2.3 Imaginal desensitization

Imaginal desensitization aims to help patients resist cue-induced craving (e.g., increasing self-control through cognitive restructuring). It is usually accomplished by exposing patients to cues (visual, auditory) to boost craving and then give them tools to help them resist gambling. There is a small line of evidence that it may be promising for GD. Firstly, imaginal desensitization with motivational interviewing showed some promise, as discussed in the previous section (Grant et al. 2009; Grant et al. 2011b). Secondly, in another study, imaginal desensitization combined with either n-acetyl cysteine or placebo over 6 weeks deceased disorder severity in patients with GD and comorbid Tobacco Use Disorder (Grant et al. 2014). However, it is difficult to discern the individual effects of imaginal desensitization, given that it was given with another treatment. More studies are thus needed to better

understand the effects of imaginal desensitization. Another approach is Gamblers Anonymous.

1.1.3.2.4 Gamblers Anonymous

Similar to Alcoholics Anonymous, Gamblers Anonymous follows a 12-step recovery program that promotes abstinence. Members attend meetings and have a sponsor that helps them with several aspects of recovery, such as helping them adjust to a gambling-free life by providing coping skills through a supportive social network, as well as helping them deal with gambling-related financial difficulties. Meetings are easily accessible and held daily across many North American cities.

Although it is difficult to assess its clinical efficacy due to its anonymous nature, RCTs do not support its effectiveness (Petry et al. 2006, Grant et al. 2009; Linardatou et al. 2014). This could be because they examined Gamblers Anonymous as a control condition (e.g., referral). For instance, patients who received an 8-week intervention combining Gamblers Anonymous and a stress management program (i.e., helping patients cope with stress, including relaxation techniques) displayed improved quality of life and mood as compared to those that attended Gamblers Anonymous over 8 weeks (Linardatou et al. 2014). Also, as previously discussed, patients responded better to combined motivational therapy and imaginal incentivization as compared to Gamblers Anonymous (Grant et al. 2009; Grant et al. 2011b). However, patients attended on average 1.1 weekly meetings of Gamblers Anonymous, which may have been insufficient to induce significant clinical benefits.

Furthermore, another study found that Gamblers Anonymous in combination with psychotherapy (Group 1: 8 sessions of in-person CBT; Group 2: a workbook with CBT exercises) over 2 months was superior to Gamblers Anonymous alone (Group 3) on reducing the number of days gambled in the last month during the treatment period (Petry et al. 2006). To note, patients in all 3 groups attended on average a similar number of Gamblers Anonymous meetings, that is about 2 meetings over 2 months. However, there may have still been some benefit for those who only

attended Gamblers Anonymous, as they still showed clinical improvements, such as decreased GD severity and gambling frequency (average number of gambling days in the last month), where the latter decreased by half over the course of 1 year (Baseline: 14.2; Month 2: 9.0; Month 2: 8.0; Month 12: 7.0). In addition, they displayed large reductions similar to the other two groups in the mean amount of money (USD) gambled per month (Baseline: $1,100; Month 1: $205; Month 2: $200; Month 12: $150). Although this seems promising, larger RCTs of Gamblers Anonymous as compared to control conditions are needed to better determine its efficacy. It will also be important to find the number of sessions (and their frequency) needed (if any) to induce clinical benefits.

1.1.3.2.5 Couples' therapy

As discussed in a previous section, quality of life is often impaired in patients and their loved ones (Potenza et al. 2019). For instance, the money lost due to gambling could bring financial strain to both the patient and their partner. Divorce rates are high as well. Thus, couples' therapy could be a good approach to treat patients and provide support to their loved ones (i.e., on other things than GD). A recent study found similar benefits of CBT to couples therapy (both delivered by internet; 10 therapist-guided sessions), where both treatments decreased depressive and anxious symptoms, gambling-related financial losses and GD severity in patients, as well as improved relationship satisfaction, which lasted at follow-up (3-, 6-, and 12-months post-treatment) (Nilsson et al. 2019). Another RCT found that 12 weekly sessions of couples' therapy as compared to control (3 brief interventions over the same timeframe) decreased gambling symptoms (e.g., urges, thoughts about gambling) in patients and reduced mental distress in their partners, which lasted at the 20-week follow-up (Lee and Awosoga 2015).

Future studies could combine couples' therapy and medications to determine whether they improve outcomes (e.g., improving adherence). Furthermore, these treatments could be proposed for other family members or close ones of the patient, since approximately six people are affected per patient (e.g., other family members,

close friends, etc.) (Goodwin et al. 2017). This could also in turn help the patient. For instance, they could help the patient maintain abstinence by providing emotional support, etc. (Kourgiantakis et al. 2013).

Altogether, there is some evidence that medications and psychotherapy hold promise. Opioid antagonists and CBT are the most promising pharmacological and behavioural treatments. However, as previously discussed, findings are mixed and there are high relapse rates. For instance, about 75% of patients relapse after 12 months of CBT (Hodgins et al. 2007). Medications can also cause side effects such as nausea, insomnia, gastrointestinal problems, and even suicidality (although they differ by medication). Undeniably, this can impact treatment adherence (Julius et al. 2009; Velligan et al. 2009). In addition, few patients seek help (Slutske 2006) or are in denial that they have a problem (Shah et al. 2019). Raising awareness about GD and its treatment options are likely good ideas. This may help reduce stigma and shame, as well as encourage patients to seek help. Thus, it is imperative that researchers and clinicians find ways to increase adherence. One way to do so might be to combine both medications and psychotherapy. For instance, a recent systematic review examining pharmacological RCTs in GD found higher rates of completion when combined with behavioural treatments (72%) as compared to medications alone (56%) (Kraus et al. 2020). In addition, many studies do not have follow up assessments, thus it would be important to include these in future studies to identify and characterise lasting effects.

Furthermore, comorbidity with other psychiatric disorders can influence adherence (Lorains et al. 2011) or response to treatment (Di Nicola et al. 2019). Hence, it is important to help patients accordingly. Patients might not all benefit from a “one size fits all” approach to treatment and comorbidities should be taken into consideration (Potenza et al. 2019; Kraus et al. 2020). Undeniably, GD is a complex disorder where several subgroups are thought to exist (Alvarez-Moya et al. 2010; Moon et al. 2017; Menchon et al. 2018). Therefore, we need to develop new treatment approaches.

Since GD is very complex, it is important to develop them based on its neurobiological substrates and to personalise these treatments.

The neurobiology of GD is purported to resemble that of SUDs, implicating the PFC and the striatum (Koehler et al. 2013; Koehler et al. 2015; Quaglieri et al. 2020; Raimo et al. 2021), as well as the insula (Mohammadi et al. 2016; Limbrick-Oldfield et al. 2017; Yip et al. 2018). However, there is emerging evidence that other regions might be implicated in gambling behaviours, such as parietal, occipital, cingulate, and temporal cortices, as well as the cerebellum (Crockford et al. 2005; Balodis et al. 2012; Brevers et al. 2016; Limbrick-Oldfield et al. 2017). Thus, to inform treatment approaches, it is crucial that we advance our understanding of neurobiological substrates.

Neural substrates can be investigated in various ways: 1) structurally, 2) functionally and 3) chemically. These approaches hold promise to develop treatments and biomarkers that could help assess etiology, disorder progression and response to treatment. Hence, it is critical to better understand these substrates, which will be explored next.

1.1.4 Neurobiological substrates

1.1.4.1 Brain morphometry

Brain morphometry refers to the size and shape of the brain (Greve 2011). Morphometry can help characterise, diagnose, and understand the progression of psychiatric disorders (Haubold et al. 2012). Structural MRI can measure morphometry (i.e., a T1-weighted image). Each MRI scan is composed of thousands of voxels. A voxel is like a 2-dimensional pixel, but it is 3-dimensional (usually 1 mm^3). Automated software can be used to measure gray matter metrics (e.g., volume) of cortical and subcortical regions, such as FreeSurfer. Structural MRI can be investigated with voxel-based morphometry and surface-based morphometry. Voxel-based morphometry was one of the first techniques studied to measure gray matter volume in ROIs (Ashburner and Friston, 2000). The main steps of its pipeline

include segmenting gray matter, white matter and cerebrospinal fluid from a T1-weighted image and transforming the images into a common stereotactic space.

Surface-based morphometry allows to measure volume of ROIs as well as properties that are specific to the cortex, such as surface area and thickness of ROIs (Dale et al. 1999 Fischl et al. 1999a; Fischl et al. 1999b). It uses an automated pipeline that constructs models of the boundaries between the white, grey, and pial surfaces, where the cortex is located between the pial and the grey/white matter boundaries. The pial surface is represented by a 2-dimensional sheet that allows to visualise the usually deep, hidden sulci (see **Figure 2**). The brain's surface is registered to a spherical atlas based on the brain's gyral and sulcal folding patterns (as seen on the T1-weighted structural scan) to accurately align anatomy. Also, the atlas' coordinate

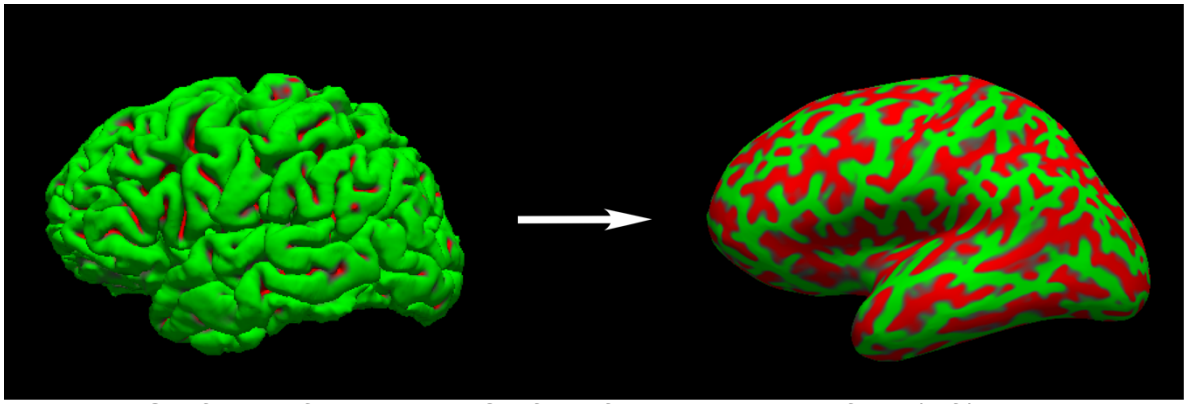

Figure 2. **Surface inflation**. FreeSurfer inflates the pial surface (left) to reveal both the gyri (green) and sulci (red).

system is used to align surfaces, which is useful for group-level analyses (to have each patient's brain in the same "space"). This cortical surface sheet contains a mesh of triangles (see **Figure 3**). Each neighboring triangle meets at a vertex and has a corresponding coordinate. Finally, algorithms label the brain with various atlases (see **Figure 4**). Importantly, its accuracy is similar to manual labeling subcortical and cortical areas (Fischl et al. 2002, Fischl et al. 2004).

Morphometric measures of living brains for regions of interest (ROIs) include surface area, thickness, and volume. Firstly, surface area is thought to reflect the number and/or spacing of cortical columns (Rakic 1988, Rakic 2009). Secondly, thickness is believed to represent neuronal density (la Fougère et al. 2011). It could also represent dendritic length. To illustrate, a study found a positive correlation between thickness and dendritic length in human brain slices (Goriounova et al. 2018).

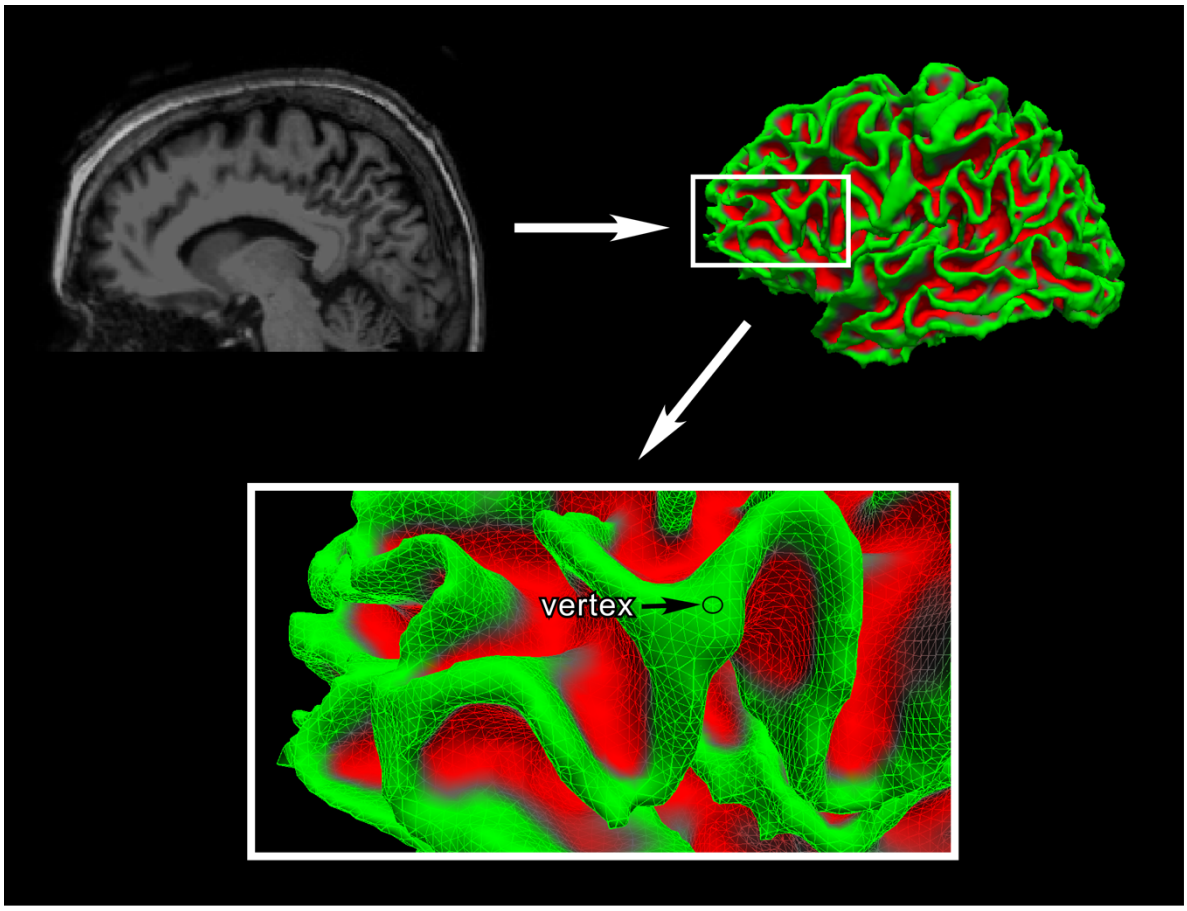

Figure 3. **Cortical mesh**. The cortex from the T1-weighted image is transformed into a surface containing a mesh of triangles that meet at different vertices.

Thirdly, volume is thought to reflect neuronal size and/or the number of neurons (de Sousa and Proulx 2014). Larger as compared to smaller volume could reflect bigger neuronal size, e.g., of soma and length of dendrites, and/or a higher number of neurons. In sum, morphometry could help better understand substrates of healthy brains and those with disorders, including GD. It could also help further our

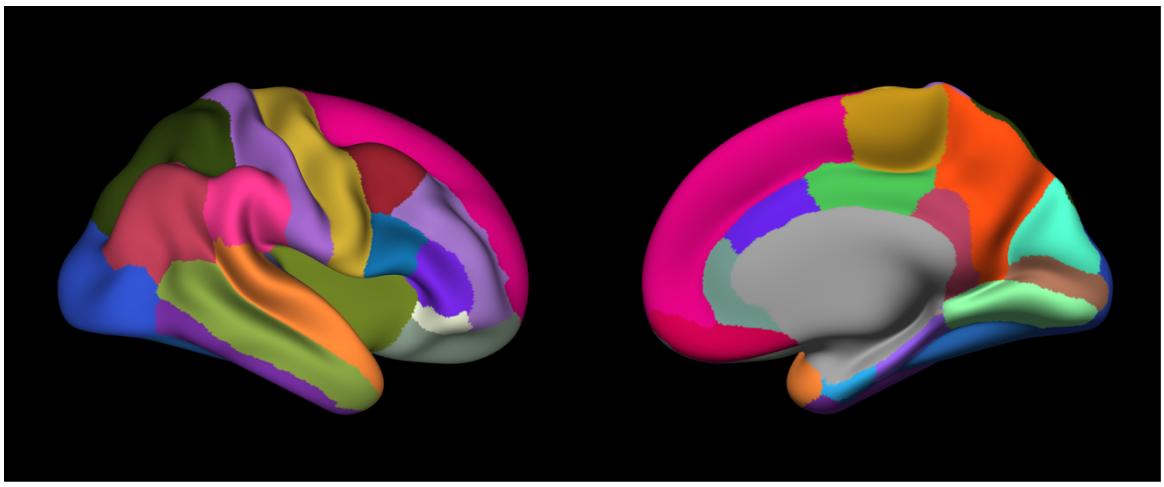

Figure 4. **Cortical atlas**. Atlases can be used to label the lateral (left) and medial (right) cortices. Shown here is a semi-inflated white matter surface.

understanding of its etiology to develop better treatments. For example, a recent study assessed brain volume in adolescents at 2 time points, i.e., 14 and 19 years of age (Kühn et al. 2019). Individuals were asked to report their alcohol use at 3 different time periods. The authors found a positive correlation between bilateral caudal and left cerebellar volumes and duration of alcohol use.

A fair number of studies assessed morphometry in patients with GD. Most used voxel-based morphometry to compare differences between GD patient groups and healthy individuals. A smaller amount used surface-based morphometry (discussed further below). Regarding voxel-based morphometry, studies mostly showed smaller volumes of cortical and subcortical ROIs. More specifically, the temporal, occipital, and parietal cortices were littler. More specifically, for the temporal cortex, volume was lower for the right inferior temporal gyrus (Mohammadi et al. 2016). In the occipital cortex, lower volumes were found in the right occipital fusiform gyrus (Mohammadi et al. 2016), as well as in the left inferior occipital gyrus, right calcarine gyrus, right cuneus, and right middle occipital gyrus (Zois et al. 2017). In addition, lower cortical volumes were reported in the left supramarginal gyrus (Takeuchi et al. 2017), bilateral insula (Mohammadi et al. 2016), and right and/or left anterior cingulate cortex (Mohammadi et al. 2016; Zois et al. 2017).

Furthermore, both higher and lower volumes of the prefrontal cortex (PFC) and frontal cortex were found. Right middle frontal volume was greater (Koehler et al. 2015). Volumes of the bilateral superior medial frontal cortex (Zois et al. 2017), rectal gyrus (Takeuchi et al. 2017) and dorsomedial PFC were smaller (Ruiz de Lara et al. 2018). In addition, the right ventrolateral and ventromedial PFCs were thinner (Raimo et al. 2021). Studies also reported smaller volumes of the right orbitofrontal (Mohammadi et al. 2016) and left middle orbitofrontal cortex (Takeuchi et al. 2017). Regarding other frontal regions, the left inferior frontal gyrus (IFG) was smaller (Zois et al. 2017), whereas right IFG volume was larger (Irizar et al. 2020). Also, the right precentral gyrus and bilateral supplementary motor areas had smaller volumes (Mohammadi et al. 2016).

Finally, subcortical areas were mainly smaller in patients with GD. Volumes were lower for the left or right hippocampus (Mohammadi et al. 2016), left or right amygdala (Mohammadi et al. 2016; Takeuchi et al. 2019), as well as the bilateral putamen (Mohammadi et al. 2016). In addition, right ventral striatal volume was larger (Koehler et al. 2015). Further, the bilateral posterior cerebellum was smaller (Takeuchi et al. 2017). Lastly, it should be noted that some studies found no gray matter differences between patients and healthy individuals (Joutsa et al. 2011; van Holst et al. 2012; Yip et al. 2018; Freinhofer et al. 2020).

Altogether, it appears that studies using voxel-based morphometry mainly found smaller volumes of various regions across the brain, although results are less consistent for frontal and subcortical structures. Strengths of these studies include assessing morphometry in various regions, yet the clinical relevance is unclear. Some of these studies investigated this and found links between cognitive symptoms and various cortical and subcortical ROIs. First, one study found a negative correlation between negative urgency (negative urgency subscale of the UPPS-P Impulsive Behavior Scale) and volume of the right ventrolateral PFC (middle frontal gyrus extending into the orbital gyrus) (Ruiz de Lara et al. 2018). Second, volume of the bilateral dorsal anterior cingulate cortex negatively correlated with cognitive

distortions (Interpretative Bias subscale of the Gambling-Related Cognition Scale) (Ruiz de Lara et al. 2018). Third, bilateral medial orbitofrontal (gyrus rectus) volume positively correlated with higher expected value sensitivity, reflecting better decision making (Cups task) (Freinhofer et al. 2020). In addition, left amygdalar volume negatively correlated with risky probability cognition (Takeuchi et al. 2019).

Moreover, positive correlations were reported between volumes of the left insula, left orbital frontal cortex and right lateral occipital cortex, as well as a negative correlation with left frontal pole/superior frontal gyrus volume (Mohammadi et al. 2016). However, the clinical relevance is unclear given that these correlations were also present in healthy individuals. Another study found negative correlations between impulsivity (Barratt Impulsiveness scale), more specifically with volumes of the right parietal cortex (superior parietal lobule, precuneus, postcentral gyrus, angular gyrus), bilateral operculum (left rolandic and central, right parietal), left precentral gyrus, right superior temporal gyrus, bilateral insula, right cerebellum, bilateral parahippocampal gyrus, bilateral amygdala, and bilateral hippocampus (Yip et al. 2018). To note, the correlations in this study were also significant in healthy individuals and patients with Cocaine Use Disorder (Yip et al. 2018). Lastly, superior medial frontal volume positively correlated with average number of gambling hours per day (Zois et al. 2017).

Regarding surface-based morphometry, studies mainly assessed volume or thickness and found smaller morphometric measures of various ROIs in patients with GD as compared to healthy individuals. One study found lower thickness predominantly in right cortical regions, such as the right superior frontal cortex, right medial orbitofrontal cortex, and the right rostral middle frontal gyrus (including a portion of the right dorsolateral prefrontal cortex (DLPFC)) (Grant et al. 2015). They also reported a thinner parietal cortex, specifically the right supramarginal gyrus, right postcentral gyrus, and the left inferior parietal cortex. Some other studies found smaller volumes of subcortical areas, more specifically of the right amygdala and left hippocampus (Rahman et al. 2014), as well as the left putamen, right hippocampus,

and right thalamus (Fuentes et al. 2015). One of these studies also used a whole-brain approach which yielded no differences (Fuentes et al. 2015). None of these studies found associations between morphometric measures and clinical and cognitive measures that survived corrections for multiple comparisons.

More recent studies investigated other surface-based measures, i.e., cortical folding patterns and curvature. One study assessed the sulcal and gyral folding patterns of the orbitofrontal cortex (Li et al. 2019). Patients with GD had a different orbitofrontal folding pattern compared to healthy individuals. Lastly, a study evaluated curvature of the striatum. Differences were found in the bilateral pallidum and left putamen between patients with GD and individuals with GD symptoms as compared to healthy individuals. Also, this study reported a negative correlation between right globus pallidum mean curvature and impulsivity level (impulsivity subscale score of the Eysenck Impulsivity Questionnaire), in both patients with GD and individuals with symptoms of GD (Grant et al. 2019). The authors thus proposed that curvature of this region may be a predisposition for GD development, since impulsivity can predict the onset of GD (Shenassa et al. 2012).

As one can see, most studies assessed differences in specific ROIs between patients with GD and healthy individuals using voxel-based morphometry. Strengths of these studies include assessing morphometry in various brain regions in GD, thereby helping bridge the gap between the lack of knowledge in GD as compared to SUDs. However, few studies investigated surface-based morphometric measures, despite their relevance to understanding the neural substrates of GD. It thus seems important to investigate differences in surface-based morphometry across the whole brain in patients with GD as compared to healthy individuals.

In addition, most studies did not assess the relationship between morphometry and clinical or cognitive variables. There were also no links involving surface-based morphometric measures of thickness and surface area in GD. Hence, it appears important to further assess whether morphometric measures (including surface-

based metrics) are related to the clinical profile. Doing so could provide additional, complementary information other than solely comparing to healthy individuals. Therefore, future studies should test for correlations with clinical and cognitive measures, such as impulsivity, which may predict both susceptibility to the disorder and relapse. This pertains to GD and disorders sharing similar substrates, such as SUDs. It also seems pertinent to study brain function in GD, which is discussed next.

1.1.4.2 Resting state functional connectivity

Resting state functional connectivity (rs-FC) is a type of functional magnetic resonance imaging (fMRI) that measures brain function in the absence of a task. More specifically, it allows to investigate the intrinsic, spontaneous fluctuations of the fMRI "Blood Oxygen Level Dependent" (BOLD) signal (Bijsterbosch et al. 2017; Lv et al. 2018) (see **Figure 5**). rs-FC is defined as the temporal correlation of the BOLD signal between different brain regions (Bijsterbosch et al. 2017) (see **Figure 6a**). We

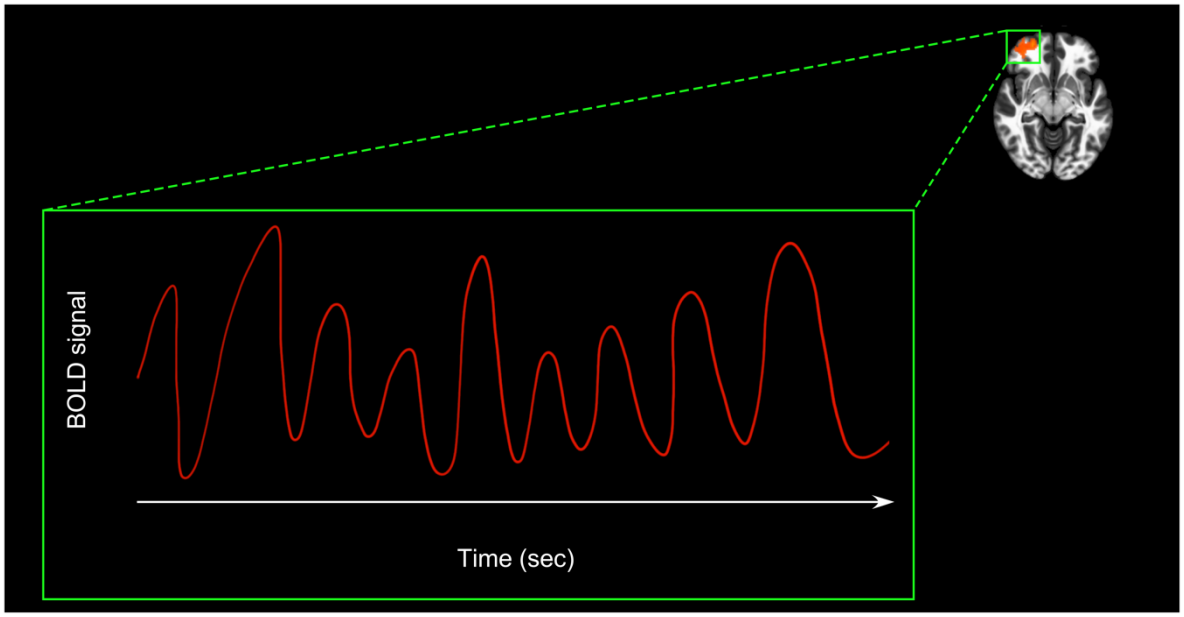

Figure 5. **The BOLD signal**. A close-up illustration of the BOLD signal is demonstrated in a prefrontal area.

can also study a resting state network, which is a set of brain areas that have similar intrinsic BOLD signal patterns during rest (Bijsterbosch et al. 2017).

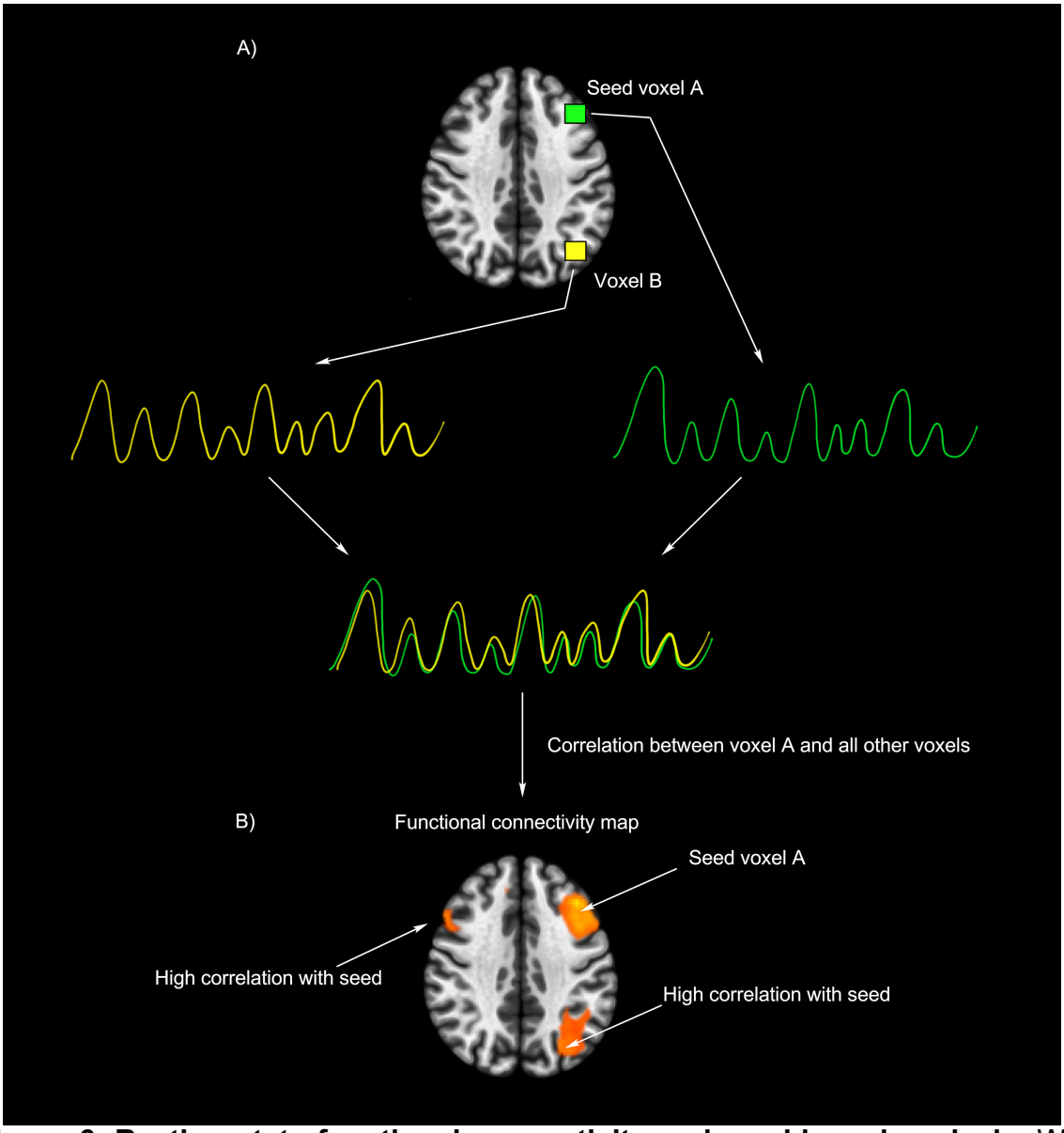

Figure 6. **Resting state functional connectivity and seed-based analysis**. We can study the resting state functional connectivity between regions. In this example, A) voxel A and voxel B display an intrinsic functional connectivity (their BOLD signals are similar and highly correlated), thus these two voxels functionally connected. We can examine resting state functional connectivity between a seed (i.e., a ROI) and the rest of the brain, also known as seed-based analysis. B) Shown here is an example of a functional connectivity map that one could obtain with this analysis.

There has been increasing interest over the last 10 years to use rs-FC to examine the neural substrates of various clinical populations (Zhang et al. 2021), including SRADs (e.g., Fedota and Stein 2015; Sutherland and Stein 2018; Thomson et al. 2022; Yan et al. 2021; Zhang and Volkow 2019). This is largely because rs-FC offers

several promises that could help elucidate the neural substrates of several clinical populations (Bijsterbosch et al. 2017; Zhang et al. 2021). First, rs-FC is practical since it is fast (5-10 min) and easy (task independent) to acquire. This is advantageous, as it is accessible to a wide range of clinical populations, including those that cannot easily perform tasks (e.g., patients with cognitive impairments), in addition to pediatric populations (e.g., infants).

Second, rs-FC is reliable, but plastic. Its stability thus allows to examine how behavioural, pharmacological, and non-invasive neuromodulation interventions can modulate it. For example, rs-FC could serve as a treatment target or as a baseline assessment to predict who may or may not respond to treatment. It should be noted that rs-FC of circuits can be measured regardless of how the participant's mind is wandering or their state. For instance, the strength of functional connectivity can differ based on the state of patients with SUDs (e.g., abstinence/craving, satiety), but rs-FC is still measurable nonetheless (e.g., Fedota and Stein 2015; Sutherland and Stein 2018; Zhang and Volkow 2019). Third, its ease of acquisition supports multidisciplinary "big data" efforts to collect and share large datasets of both healthy and diseased brains, with the ultimate long-term goals of finding biomarkers, as well as monitoring or predicting the progression of disorders (e.g., Human Connectome Project: https://nda.nih.gov/ccf/; https://www.humanconnectome.org).

Most studies assessed rs-FC in GD using seed-based (ROI) analyses (see **Figure 6b**). Seed-based analysis assesses the connectivity between the seed and every other voxel in the brain (Lv et al. 2018; Nieto-Castañon 2020). Firstly, one study investigated rs-FC of 2 ROIs, that is, the right middle frontal gyrus and the right ventral striatum (Koehler et al. 2013). The PFC seed displayed stronger rs-FC with the right striatum and weaker connectivity with the bilateral superior frontal gyrus and paracingulate gyrus in patients with GD as compared to healthy individuals. The striatal seed showed increased rs-FC with the left cerebellum and the right superior frontal gyrus, which extended to the bilateral paracingulate gyrus and the right middle frontal gyrus.

Another study examined rs-FC of a posterior cingulate cortex seed, whose functional connectivity was weaker with 3 regions, that is, the precuneus, left medial superior frontal gyrus and right middle temporal gyrus, in patients with GD as compared to healthy individuals (Jung et al. 2014). One study investigated 5 seeds, i.e., right amygdala, right orbitofrontal cortex, left thalamus and left/right caudate nucleus (Contreras-Rodriguez et al. 2016). Patients with GD displayed significant results for the orbitofrontal and amygdalar seeds, that is, greater rs-FC between the orbitofrontal cortex seed and the orbitofrontal cortex, medial frontal cortex, and the basal ganglia in comparison to healthy individuals. In addition, patients displayed greater rs-FC between the amygdala seed and the amygdala, insula, and sensorimotor cortex. They also displayed decreased rs-FC between the amygdala seed and the cerebellum and the posterior cingulate cortex.

Furthermore, another study investigated 6 seeds, i.e., the bilateral posterior cingulate cortex, DLPFC, and amygdala (Bae et al. 2017). rs-FC of the left posterior cingulate cortex seed was strongly connected to the right superior temporal and left anterior cingulate gyri as compared to healthy individuals. The right posterior cingulate cortex seed displayed increased rs-FC with the right precuneus. Also, the left DLPFC seed demonstrated weaker rs-FC with the bilateral postcentral gyrus and the right precentral gyrus. The left amygdala displayed increased rs-FC with the right middle frontal gyrus. The right amygdala showed stronger rs-FC with the right superior frontal gyrus. Lastly, a study investigated rs-FC between an insular seed and a default mode network (Tsurumi et al. 2020). They reported increased rs-FC between the insula and two regions in patients as compared to healthy individuals, i.e., the medial PFC and the temporal-parietal junction of the default mode network.

Some of these studies found relationships between rs-FC and clinical or cognitive variables. More specifically, rs-FC between the right middle frontal gyrus seed and the striatum correlated with impulsivity, craving, and tobacco smoking habits (Koehler et al. 2013). In addition, there was a positive correlation between rs-FC of the striatal seed and the cerebellum with smoking habits (Koehler et al. 2013). Also,

rs-FC between the posterior cingulate and precuneus was negatively correlated with GD symptom severity (Jung et al. 2014). Further, rs-FC between the right posterior cingulate cortex seed and right precuneus negatively correlated with GD severity (Bae et al. 2017). Lastly, there was a positive correlation between duration (months) of GD and rs-FC between circuits involving the insula and the medial PFC, as well as the temporo-parietal junction (Tsurumi et al. 2020).

As one can see, many circuits containing different regions seem important for GD, including prefrontal and striatal regions. Strengths of these studies include assessing rs-FC of different regions in GD (i.e., since not much is known regarding rs-FC in GD). However, there are inconsistencies between studies, which may be due to the methods used. For instance, seed-based analyses can be biased since the results depend on the seed choice (Lv et al. 2018). It thus seems important to consider examining the entire brain to complement the findings from these studies and help identify novel substrates that might not otherwise have been considered. To this end, a small number of studies used whole-brain approaches to study rs-FC in GD, more specifically, using independent component analysis and graph theoretical analysis, which will be explored next.

Independent component analysis (ICA) separates the whole-brain BOLD signal into independent spatial components (networks) that are temporally correlated (Lv et al. 2018). Each network contains synchronized BOLD activity (see **Figure 7**). It appears that two studies investigated rs-FC in GD using ICA. The first study found that patients with GD displayed stronger rs-FC of a ventral attention network (implicated in salience) which included mostly the right insula, as compared to healthy individuals (van Timmeren et al. 2018). The other study found that patients with GD had greater rs-FC of a reward, occipital, and cerebellar network in comparison to healthy individuals (Piccoli et al. 2020).

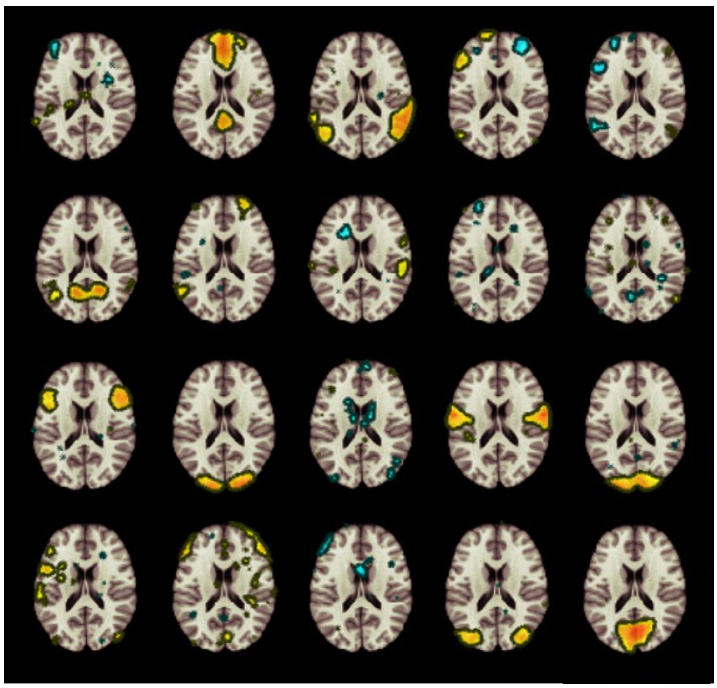

Figure 7. **Independent component analysis**. ICA is a data-driven approach that separates the BOLD signal into different components (20 components, in this example, shown axially). Hot (yellow, orange) and cold (blue) colours represent strong and weak functional connectivity, respectively of regions within the networks.

Moreover, one study examined rs-FC using region to region and graph theoretical analyses (Tschernegg et al. 2013) (the latter analysis will be discussed in the next section). Region to region analysis examines functional connectivity between pairs of regions across the entire brain (Nieto-Castañon 2020). Patients displayed stronger rs-FC between frontal regions and between frontal and temporal areas as compared to healthy individuals. They also demonstrated stronger rs-FC between the left caudate nucleus and two regions (right and left anterior cingulate cortex). In addition, patients showed weaker rs-FC between the left subcallosal cortex and the left amygdala.

Two of these studies found associations between rs-FC and measures of GD severity and cognitive control. Notably, there was a positive correlation between rs-FC of the cerebellar network and GD severity (scores on the Pathological Gambling adaptation of the Yale-Brown Obsessive-Compulsive Scale) (Piccoli et al. 2020).

The other study found a positive correlation between cognitive distortions (Gambler's Beliefs Questionnaire) and rs-FC of central executive, default mode and limbic networks (van Timmeren et al. 2018). The central executive network is implicated in cognitive functions such as planning and decision-making (Seeley et al. 2007). The main regions in this network include lateral fronto-parietal regions. The default mode network, anchored in the medial PFC and posterior cingulate cortex, is responsible for self-referential processes (Buckner et al. 2008). The limbic network is involved in memory and emotion processing and is anchored in the temporal lobe (Catani et al. 2013). The results suggest that stronger rs-FC of several networks could underlie the cognitive deficits displayed in patients with GD.

Furthermore, graph theoretical analysis measures topological properties of complex networks (undirected graphs) containing nodes (vertices or objects) and edges (bidirectional links) (Bijsterbosch et al. 2017; Lv et al. 2018) (see **Figure 8**). There is growing interest to use this approach since the brain is purported to be an intricate interconnected network. Graph theory allows to analyze region-to-region (node to node) functional connectivity (edges are suprathreshold connections). Graph theoretical analysis can study the function of neural networks as a whole (globally) or within specific areas of the network (local properties), which are known as integration and segregation, respectively. Integration is the capability for the entire neural network to exchange information, whereas segregation is the ability for nodes to efficiently transmit information to their neighbours (Latora and Marchiori 2001).

There are several graph theoretical measures that allow us to examine how each region contributes to the network (Nieto-Castañon 2018, 2020). The main measures are average path length, global efficiency, betweenness centrality, cost, degree, local efficiency, and clustering coefficient (Nieto-Castañon 2018). All except local efficiency and clustering coefficient are measures of centrality, that is, how important a node is within the architecture of the entire network (van den Heuvel and Sporns 2013). Thus, a region with high centrality is thought to interact with several other regions, as well as enable integration (Rubinov and Sporns 2010). Local efficiency

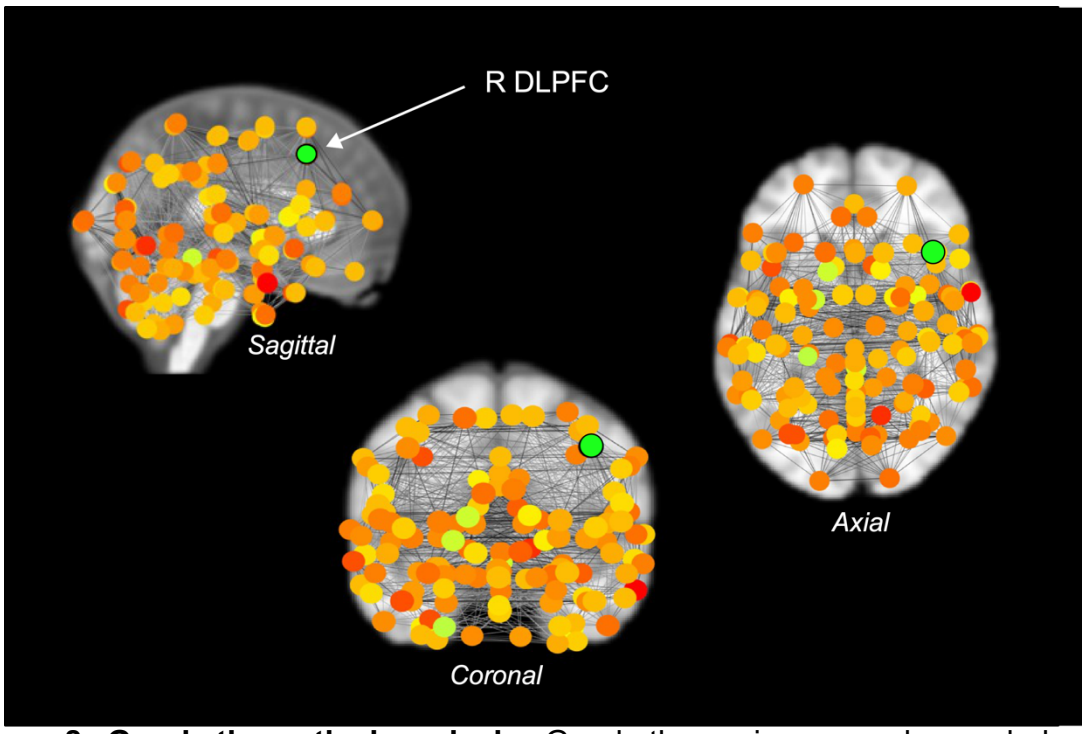

Figure 8. **Graph theoretical analysis**. Graph theory is a complex node-based analysis technique that describes a network's functioning. The brain regions (nodes) are shown in warm tones (yellow, orange, red) and the connections (edges) are grey. Shown here is the global efficiency for the right DLPFC (green) across the 3 main axial, coronal, and sagittal planes. DLPFC: dorsolateral prefrontal cortex; R: right.

and clustering coefficient are measures of locality, which will be discussed after the measures of centrality.

Firstly, average path length is the mean distance between a node and the rest of the nodes (Nieto-Castañon 2018, 2020). A region that has a lower average path length communicates more efficiently and directly with the other brain regions (Latora and Marchiori 2001; Nieto-Castañon 2020). Global efficiency is calculated as the mean inverse distance in the shortest path between a given node and all the other nodes (it is inversely related to average path length). This inversion may offer several advantages (Achard and Bullmore 2007). For instance, it provides a simpler way to estimate the efficiency of nodes that may be disconnected from applying strict thresholds to correlation matrices. In that case, the average path length between this node and the rest of the network is infinite, whereas the node's contribution to the

network's global efficiency is zero. Likewise, these calculations allow global efficiency to be weighted by the most connected regions (hubs), whereas average path length is weighted by the regions that are the least connected.

Nevertheless, it seems pertinent to consider examining both average path length and global efficiency, since they reflect different aspects of information processing that seem pertinent to understanding brain function (Klingner et al. 2016). More specifically, average path length is thought to encompass serial (sequential) processing, whereas global efficiency is believed to involve parallel (simultaneous) information processing (Townsend 1990; Achard and Bullmore 2007). Furthermore, betweenness centrality is the proportion of all the network's shortest-paths (between pairs of regions) that pass through a particular region (Nieto-Castañon 2018, 2020). Cost and degree refer to the proportion and number of regions, respectively, that are linked to a specific region.

Lastly, local efficiency and clustering coefficient reflect locality, i.e., local properties of the network. Both measures are related. Local efficiency is the global efficiency of the node's neighbouring subgraph (small, local network). A subgraph with high local efficiency is optimized and highly efficacious, compared to one with low local efficiency (Lv et al. 2018). Clustering coefficient represents the amount of local (neighbourhood) clustering (Lv et al. 2018). It is measured as the proportion of connected nodes in a local graph (neighbourhood) that only contain the neighbours of each node.

Altogether, high values for all measures reflect a high importance of a node in the overall network (except lower values for average path length), which seem important to understand brain function. Indeed, the brain is thought to have small-world properties, such that it performs in an efficient manner via nodes that work together (e.g., high levels of global efficiency, clustering coefficient and local efficiency) with few edges (small average path lengths) and with low costs. However, it is unclear whether this applies to healthy brains and/or disordered brains, as well as the

potential clinical significance for psychiatric disorders. Nevertheless, there is increasing interest to understand network organization using graph theoretical analysis in psychiatric disorders, including SRADs (Lin et al. 2015; Pandria et al. 2018).

It seems that one study investigated rs-FC using graph theoretical analyses in GD (Tschernegg et al. 2013). In this study, patients with GD displayed weaker clustering coefficients of the left juxtapositional lobule (supplementary motor area) and left paracingulate cortex versus healthy individuals. In addition, patients had weaker local efficiency of the left juxtapositional lobule. They also showed greater node betweenness (i.e., betweenness centrality) of the bilateral paracingulate cortex as compared to healthy individuals. These regions might be more central to the neural functioning of the GD brain as compared to the healthy brain, and possibly underlie maladaptive gambling behaviours such as reward expectancy and loss-chasing. However, the potential clinical relevance (e.g., testing for associations with gambling symptoms) remains to be investigated.

So far, we have explored rs-FC in patients with GD. Overall, patients with GD displayed mostly greater rs-FC across the brain (although there was weaker rs-FC between some regions) as compared to healthy individuals. Yet, it is unclear as to what higher or lower rs-FC means for GD patients. As one can see, using a data-driven approach allows the opportunity to assess rs-FC in areas not limited by a defined ROI, which can help better our understanding of the substrates. The next steps would be to assess potential correlations with clinical and cognitive measures in more studies to better understand the neurobiology of GD. It is likely also important to explore neurochemistry in GD.

1.1.4.3 Neurotransmitters

Many neurotransmitters play a role in GD, such as dopamine, gamma aminobutyric acid (GABA) and glutamate, as in SUDs (Grant et al. 2016; Clark et al. 2019). Firstly, dopamine is mainly involved in motivation, learning and reward. Although many

studies have used Positron Emission Tomography (PET), the results are inconsistent (Clark et al. 2019). Of note, gambling activity can release dopamine in the ventral striatum of patients with GD and is positively correlated with symptom severity (Joutsa et al. 2012). Neurochemical levels can also be investigated using magnetic resonance spectroscopy imaging.

Magnetic resonance spectroscopy imaging (MRSI) allows to quantify neural metabolites in a region (i.e., voxel of interest) using MRI scanners (Mescher et al. 1998). We can measure glutamate and gamma aminobutyric acid (GABA), which are the primary excitatory and inhibitory neurotransmitters, respectively. MRSI is based on the resonance frequency of metabolites that are quantified from the resonance frequency of another metabolite (e.g., water or creatine). It is difficult to measure GABA because there are nearby metabolites that can hide its signal. To overcome this challenge, the MEGA-PRESS technique (used in this thesis) was specifically developed to measure GABA (Mullins et al. 2014) (see **Figure 9**). More specifically, it applies an editing pulse so that we can detect and measure it. It also allows to measure Glx (combined glutamine and glutamate). Given the purported imbalance of Glx and GABA in the SUD brain (Moeller et al. 2016; Chen et al. 2021), one could wonder whether re-establishing glutamate and GABA levels to “normal” could improve cognitive control and alleviate symptoms in SRADS such as GD.

It seems that 2 MRSI studies found associations between GD symptoms and GABA or Glx levels. One study found negative correlations between higher GD severity (DSM-5 scores; Problem Gambling Severity Index) and lower Glx level in the dorsal anterior cingulate cortex and occipital cortex (Weidacker et al. 2020). This same study also reported a negative correlation between lower GABA level in the occipital cortex and greater impulsivity (discounting of large, delayed rewards on a delay discounting task) in patients with GD. The other study found three positive correlations between greater neurotransmitter levels of the anterior cingulate cortex and higher impulsivity levels (Weidacker et al. 2021). More specifically, higher Glx and GABA levels were correlated with larger errors on the Stop Signal Task (which

measures the incapacity to stop prepotent responses). In addition, greater Glx level was correlated with larger incongruent errors on the Eriksen Flanker Task (which assesses the inability to resist interference from distractors). Taken together, these studies suggest a potential role of the anterior cingulate and occipital cortices for GD severity and impulsivity, which should be investigated in future work.

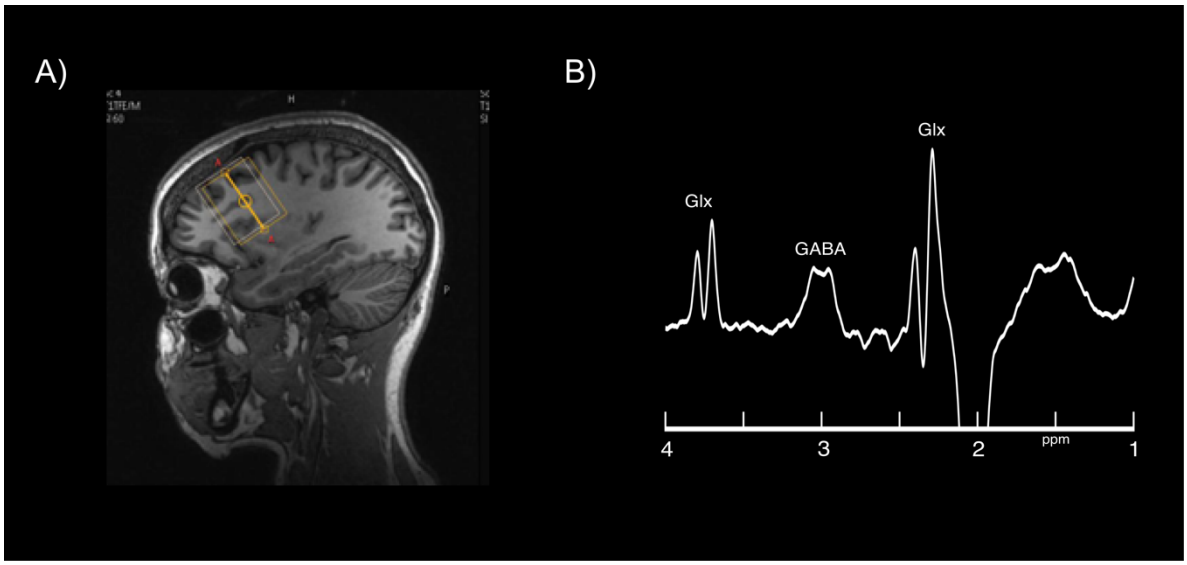

Figure 9. Magnetic resonance spectroscopy. Here is an example of A) Data acquisition in a voxel of interest in the prefrontal cortex and B) quantification of GABA and Glx using the MEGA-PRESS sequence. (PPM = parts per million; a measure of frequency). Figure 9b is reproduced with permission from Dr. Richard Edden, Professor of Radiology and Radiological Science at Johns Hopkins University School of Medicine, U.S.A.

In sum, few studies have examined the brain substrates of GD. There are however many inconsistencies regarding the findings. More research is needed to better understand brain substrates relevant to GD. Also, it would be useful to test for associations with clinical and cognitive symptoms, e.g., impulsivity and GD severity. Doing so could help establish which substrates are best to target with treatments. One possible therapeutic avenue that can target neurobiological substrates is non-invasive neuromodulation.

1.2 The clinical potential of non-invasive neuromodulation in gambling disorder

There is a whole world of non-invasive neuromodulation that may serve to help treat patients that do not respond to medications and psychotherapy. There are two major groups of non-invasive neuromodulation, which are repetitive transcranial magnetic stimulation (rTMS; see **Figure 10**) and transcranial electrical stimulation. Both are safe techniques that can target regions as well as substrates of psychiatric disorders,

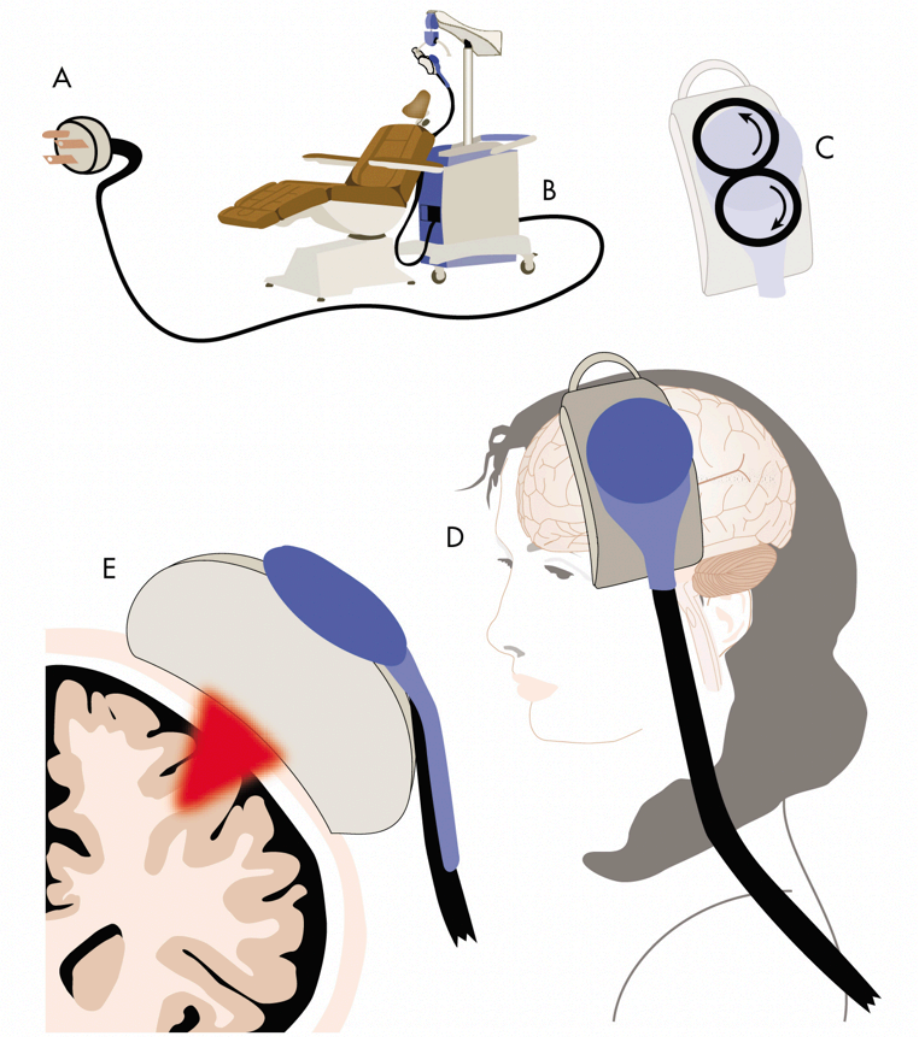

Figure 10. **Repetitive transcranial magnetic stimulation**. Alternating current (A) charges a bank of capacitators (B), generating current in the device's coils (C), which in turn produce a magnetic charge. The TMS coil is placed over the patient's left prefrontal cortex (D). The electrical charge quickly discharges through the coil and creates a magnetic field that travels through the patient's skull, which in turn creates an electric current in the brain area below the coil (E). *Reprinted with permission from Brain Stimulation Therapies for Clinicians, (Copyright ©2020). American Psychiatric Association. All Rights Reserved.*

including SRADs, to alleviate symptoms such as craving and promote abstinence.

Both techniques hold promise to target symptoms in GD, although the literature is scarce (see, e.g., reviews by Pettorruso et al. 2020, Zucchella et al. 2020). Yet, more studies are warranted since the studies employed different methods (e.g., rTMS protocols, outcome measures) and some were uncontrolled (i.e., no sham condition).

rTMS is a non-invasive neuromodulation technique that applies magnetic pulses to the scalp to reach the brain (Higgins and George 2020). The magnetic pulses create electric currents (via electromagnetic induction) that influence neuronal firing. Repeated TMS (rTMS) pulses are applied at different frequencies, which influence neuronal activity. Intermittent Theta Burst Stimulation (iTBS) and Concurrent Theta Burst Stimulation are types of rTMS that apply theta burst frequencies (i.e., a triplet at 50 Hz that is repeated at 5 Hz). All these approaches are safe and have no long-lasting side effects (mostly headaches; rarely, it can induce a seizure). rTMS is approved in both Canada and the USA for Major Depressive Disorder (MDD). More recently, rTMS was cleared in the USA for treatment-resistant OCD and smoking cessation. These approvals seem pertinent for GD, given that it was previously considered an impulse control disorder and shares symptoms including impulsivity and compulsivity with OCD, as well as sharing substrates with SUDs including Tobacco Use Disorder.

Furthermore, transcranial direct current stimulation (tDCS; see **Figure 11**) is a type of transcranial electrical stimulation that is being increasingly studied in SRADs. tDCS consists of placing at least two electrodes on the scalp and connecting them to a stimulator that delivers a constant, low amplitude current (0.5 to 4 mA) (Gandiga et al. 2006; Bikson et al. 2016; Nitsche and Bikson 2017). tDCS is based on the decades-old observation that low amplitude current can modulate brain activity (Purpura and McMurtry 1965). tDCS is easy to administer, low cost, non-invasive, painless, and safe (Antal et al. 2017). Also, it has few mild side effects (e.g., tingling

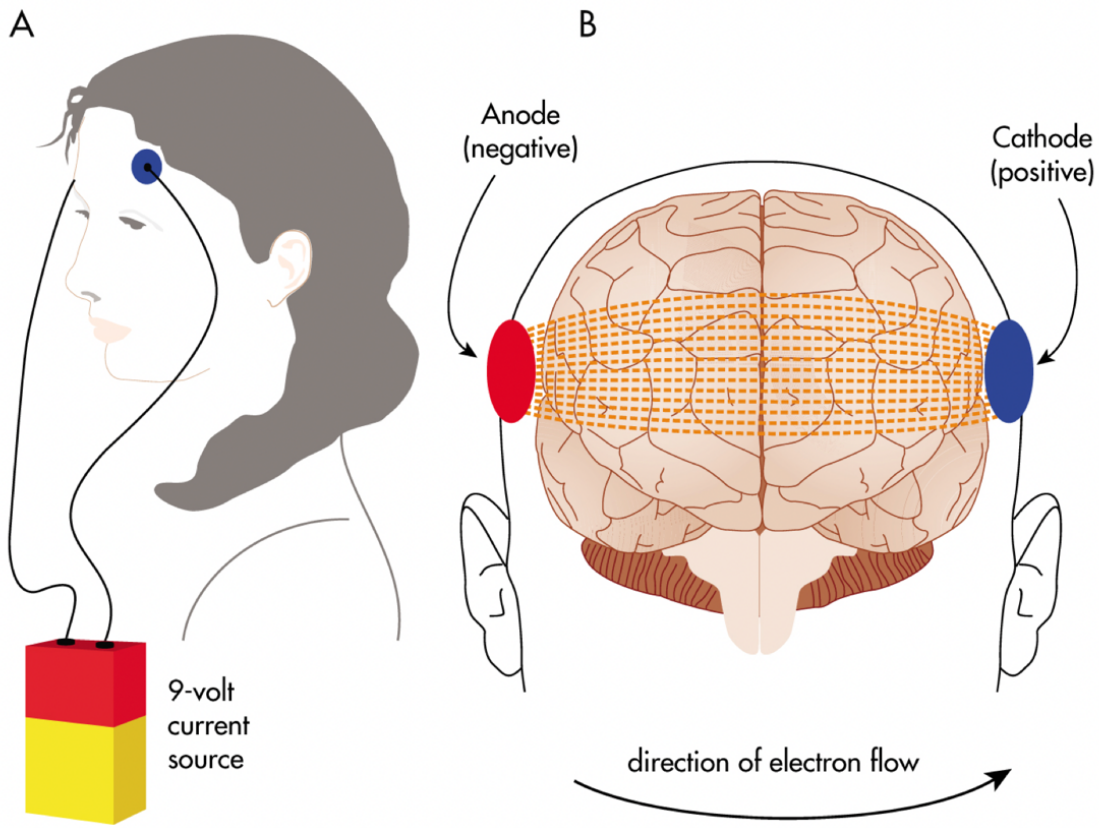

Figure 11. **Transcranial direct current stimulation**. A) Transcranial direct current stimulation is administered by applying at least 2 electrodes (i.e., anode is red, cathode is blue) over the person's scalp and are secured using a band. The electrodes are connected to a current source. B) Illustration showing the current flow from the anode to the cathode. *Reprinted with permission from Brain Stimulation Therapies for Clinicians, (Copyright ©2020). American Psychiatric Association. All Rights Reserved.*

under the electrodes during the stimulation is the most common side effect). In addition, there is a good tDCS placebo procedure, allowing for randomized, blinded, sham-controlled studies (Gandiga et al. 2006).

There are no permanent approvals for tDCS at the moment, but it was temporarily approved in the USA at the beginning of the COVID-19 pandemic for patients with MDD that were already receiving rTMS in clinical settings, so that they could continue receiving care at home. tDCS offers several advantages than rTMS, i.e., it is easier to use, has a lower cost and fewer side effects, as well as greater portability. tDCS is particularly interesting as a home-based treatment, which has the potential

to reach more patients (e.g., for those living far away from clinics, during COVID-19 pandemic). There are recent data showing tolerability and feasibility for remotely supervised home-based tDCS in 308 patients with neurological disorders (mostly Multiple Sclerosis), whom each received a mean of 23 sessions (Pilloni et al. 2022).

1.2.1 tDCS can target brain function and chemistry in healthy individuals that are relevant to gambling disorder

tDCS can modulate brain function and neurochemistry of regions or circuits that are relevant to the pathophysiology of GD. The following sections will discuss the effects of tDCS on neural substrates (rs-FC and neurochemistry using MRSI) in healthy individuals and patients with SRADs, starting with the former.

It is only in the past 10 years that studies have investigated the effects of tDCS on substrates such as rs-FC. All these studies reported tDCS-induced effects when comparing before and after stimulation, unless otherwise stated. They were also sham-controlled. Most studies examined the effects of tDCS while targeting the frontal cortex (most often the PFC) and the sensorimotor cortex, but some targeted other regions such as the cerebellum.

Most studies targeted the frontal cortex in healthy individuals. Some studies used seed-based analyses, whereas some used data-driven approaches. One study found that tDCS increased rs-FC between the right DLPFC seed (under the cathode) and the subgenual anterior cingulate cortex (Mezger et al. 2021). One study demonstrated that tDCS increased rs-FC between the left DLPFC seed (under the anode) and several regions of the right hemisphere, including the thalamus, PFC, IFG, and temporal cortex (Park et al. 2013). There was also a decrease in rs-FC between the same seed and the bilateral cerebellum, as well as the left middle frontal gyrus and IFG (Park et al. 2013). Another study found tDCS-induced elevated rs-FC between a left DLPFC seed (under the anode) and a fronto-parietal network (Kim et al. 2021).

Moreover, a study reported several tDCS-induced modulations (increased or decreased rs-FC) between two right thalamus seeds and regions including the primary motor cortex and DLPFC, as well as occipital, temporal, and cingulate areas (Sankarasubramanian et al. 2017). In addition, a study found increased rs-FC between a thalamus seed and the caudate nucleus as well as the temporal cortex (Dalong et al. 2020). One study found increased tDCS-induced rs-FC between a right inferior frontal seed (under the anode) and the bilateral caudate nucleus, as well as reduced rs-FC between the same seed and the DLPFC and parietal regions (Sandrini et al. 2020). One study found increased tDCS-induced rs-FC between the left DLPFC seed (under the anode) and the parietal cortex during and after stimulation (Mondino et al. 2020).

The other studies used data-driven methods such as ICA or graph theoretical analysis. Regarding ICA, studies reported modulation of default mode or fronto-parietal networks. Two studies found increased tDCS-induced rs-FC of a default mode network, that is, during (Abellaneda-Perez et al. 2019) and after stimulation (Keeser et al. 2011). Two studies found mixed findings, that is, tDCS-induced elevations and reductions in rs-FC of regions within a default mode network (Ahn et al. 2018; Wörsching et al. 2017). In addition, a study found that tDCS weakened rs-FC of a default mode network (Peña-Gómez et al. 2012). Another study found both reductions and elevations of rs-FC of the fronto-parietal network (Wörsching et al. 2017), whereas two studies found strengthened rs-FC of this network (Keeser et al., 2011; Peña-Gómez et al. 2012).

Furthermore, a study found tDCS-induced modulations of rs-FC patterns of the right superior temporal gyrus, left supramarginal gyrus and left superior parietal lobule (no inferences regarding the direction of the effects could be inferred, since they used a technique called multivariate pattern analysis) (Möller et al. 2017). One study found no significant effects of tDCS on rs-FC during or after stimulation, although there was a trend for increased rs-FC of the left medial PFC (Wörsching et al. 2018). Lastly, three studies used graph theoretical measures. One found increased global

efficiency of the thalamus (Dalong et al. 2020). The others reported tDCS-induced effects on centrality measures of frontal, insular, cingular, temporal, parietal, and occipital regions during stimulation (Meinzer et al. 2013; Meinzer et al. 2012).

So far, we have explored the effects of tDCS on rs-FC in studies that targeted the frontal cortex in healthy adults. As one can see, tDCS can modulate rs-FC across the entire brain. Results seem very different between studies, which is likely due to the different stimulation parameters and analysis methods. The next sections describe the effects of tDCS while targeting other regions, such as the sensorimotor cortex, cerebellum, and parietal cortex.

Some studies delivered tDCS over the sensorimotor cortex. tDCS strengthened rs-FC under the electrodes, i.e., in primary motor and/or supplementary motor areas (Amadi et al. 2014; Bachtiar et al. 2015). One study found that tDCS increased rs-FC of the primary motor cortex during stimulation but decreased it after stimulation (Sehm et al. 2013). Another reported that tDCS decreased rs-FC of the sensorimotor cortex during stimulation (Antonenko et al. 2017). Other studies reported tDCS-induced modulations of regions distal to the electrodes. One study found tDCS-induced modulations (increases or decreases) of rs-FC between two thalamus seeds and the sensorimotor cortex, insula, occipital, cingulate and/or temporal cortex (Sankarasubramanian et al. 2017). Another study reported tDCS-induced increased rs-FC between thalamus seeds and the primary motor or prefrontal regions, as well as between striatum seeds and parietal, posterior cingulate or primary motor regions (Polania et al. 2012b). One study found that tDCS modulated (increased or decreased) rs-FC between paracentral lobule seeds and cingulate, frontal, occipital, or parietal areas (Antonenko et al. 2018a). In addition, one study found that tDCS increased rs-FC between a left sensorimotor seed and left sensorimotor, motor (premotor and motor cortex) and parietal regions (Polania et al. 2011). This study also reported that tDCS increased rs-FC between a right DLPFC seed and the right insula (Polania et al. 2011).

Moreover, a study found tDCS-induced increased rs-FC of ICA-derived motor and default mode networks (Amadi et al. 2014). Some studies also found modulations (increased or decreased rs-FC) of graph theoretical measures in several regions across the brain, such as parietal, occipital, temporal, cingular, frontal, sensorimotor, striatal, insular and/or cerebellar regions during and/or after stimulation (Lindenberg et al. 2016, Lindenberg et al. 2013; Sehm et al. 2012; Polania et al. 2012a; Polania et al. 2011; Antonenko et al. 2018a).

Next, targeting the cerebellum modulated (mostly increased) rs-FC between cerebellar seeds (under the anode) and parietal, frontal, cingular, occipital, cerebellar and/or temporal regions (Turkeltaub et al. 2016; D'Mello et al. 2017; Grami et al. 2021). In addition, one of these studies reported tDCS-induced increased rs-FC between a left inferior frontal gyrus seed and the left supramarginal gyrus (D'Mello et al. 2017). It also found tDCS-induced increased rs-FC between a left parieto-temporal (supramarginal gyrus, superior temporal gyrus) seed and frontal, parietal, occipital, and temporal regions (D'Mello et al. 2017).

Furthermore, targeting the parietal cortex modulated rs-FC in circuits implicating the regions under as well as distal to the electrodes. For example, one study found tDCS-induced increases in rs-FC between a precuneus seed and the substantia nigra, as well as the insula and cerebellum, which were positively correlated with behavioural performance on a visual search task (Callan et al. 2016). Another study found that tDCS modulated rs-FC patterns of the right superior temporal gyrus and left superior parietal lobule (using multivariate pattern analysis) (Möller et al. 2017). One study found no differences in rs-FC using four default mode network seeds (bilateral parietal, medial PFC and posterior cingulate), but reported modulation of effective connectivity (which allows to investigate afferent and efferent connectivity) between these regions (Kajimura et al. 2016). Lastly, a study targeted the temporoparietal cortex and found that tDCS increased rs-FC between a right middle temporal gyrus seed and an ICA-derived default mode network as well as within the default mode network (Antonenko et al. 2018b).

In sum, these findings mostly demonstrate that tDCS can influence rs-FC of networks, including regions distal to the electrodes. Importantly, it can do so in circuits that are relevant to GD. Thus, it would be worth assessing whether tDCS can target networks of interest in patients with GD, and whether this alleviates symptoms. The next section will discuss work that investigated tDCS-induced effects on neurochemistry using MRSI.

Several studies examined the effects of tDCS on GABA and/or Glx levels in healthy adults. They targeted many regions, such as motor, parietal, temporal, cerebellar, and prefrontal areas. They compared the effects before and after stimulation (unless mentioned otherwise). Firstly, a high number of studies targeted the primary motor cortex and found reductions in GABA levels after stimulation under the anode (Stagg et al. 2011; Kim et al. 2014; Bachtiar et al. 2015; Bachtiar et al. 2018; Patel et al. 2019; Antonenko et al. 2017) or under both electrodes (Stagg et al. 2009; Antonenko et al. 2019). Some also found decreases in glutamate (Antonenko et al. 2019) and Glx (Stagg et al. 2009) levels after stimulation under the cathode.

However, some studies found no find changes in neurotransmitter levels under the anode (Rango et al. 2008; Tremblay et al. 2016; King et al. 2020) or cathode (Ryan et al. 2018; Zappasodi et al. 2018). This might be due to methodological differences. For instance, Ryan et al. (2018) used a 7 Tesla MR scanner (a much stronger magnet than the 3 Tesla MR scanners typically used in studies; the 7T scanner allows to measure glutamate), but they still reported some evidence of neurometabolite modulation. More specifically, they found a positive correlation between the changes in absolute concentrations of n-acetylaspartate and creatine, metabolites that are markers of neurometabolism. Thus, the authors propose that tDCS could still influence the brain. One study also suggested too much variability in tDCS responses or insufficient methods to measure effects (Tremblay et al. 2016). In addition, insignificant effects were unsurprising in another study since the cathodal electrode was over the motor cortex and the anodal electrode was over the shoulder

(Zappasodi et al. 2018) (typically the anodal electrode needs to be placed over the cortex as well to induce significant effects on the brain).

Fewer studies used tDCS to target parietal, temporal, cerebellar, and frontal areas. Some studies targeted the parietal lobe, which resulted in higher Glx levels under the anode (Hunter et al. 2015; Clark et al. 2011). In addition, others found reductions in GABA levels under the anode during stimulation while targeting the temporal cortex (Barron et al. 2016; Koolschijn et al. 2019). One of these studies also found increased Glx under the anode (Barron et al. 2016). Another study did not report differences in GABA or Glx (Dwyer et al. 2019) while targeting the same region. Moreover, a study targeted the right posterior cerebellar cortex and did not find any changes in GABA or glutamate under the anode during or after stimulation, possibly due to high between-subject variability (e.g., changes ranged from a 90% increase to a 100% reduction for GABA levels from before to during stimulation) (Jalali et al. 2018).

Lastly, a small number of studies targeted the bilateral DLPFC by placing the anodal and cathodal electrodes over the left and right DLPFC, respectively in healthy adults. One study found that tDCS increased Glx levels in the left striatum during stimulation (Hone-Blanchet et al. 2016). Although they did not identify tDCS-induced changes of Glx in the PFC, they found significant tDCS-induced elevation in the left DLPFC of a neural metabolite that is important for neuronal health called n-acetyl-aspartate. Another study reported tDCS-induced elevations of GABA levels in the left striatum as well as reductions in GABA levels in the right striatum and left DLPFC (Bunai et al. 2021). Lastly, there is a study that found no tDCS-induced changes in Glx or GABA levels in the right DLPFC (Mezger et al. 2021).

Altogether, most studies show that tDCS can modulate rs-FC of regions across the entire brain and that it can modulate neurotransmitters in regions close to the electrodes. Two studies found that targeting the bilateral DLPFC can modulate neurotransmitter levels in striatal regions that are away from the electrodes. These

studies are important since modulating such circuits is relevant to SRADs, including GD. The next sections will describe studies that have investigated tDCS-induced effects on rs-FC and neurotransmitters in patients with SRADs.

1.2.2 tDCS can target function and chemistry in the brains of patients with substance-related and addictive disorders

tDCS can target brain regions relevant to SRADs. The DLPFC is the most targeted region (Ekhtiari et al. 2019). Studies targeted either one DLPFC or both. Both montages can modulate function. For example, a single session of tDCS targeting the left DLPFC (anodal electrode over the left DLPFC, cathodal electrode over the right orbitofrontal cortex) strengthened functional connectivity between a right orbitofrontal cortex seed and the left DLPFC in tobacco smokers while they underwent a cue-reactivity task as compared to sham, however craving did not change (Kroczek et al. 2016). In addition, another study found that 10 tDCS sessions targeting the right DLPFC (anodal electrode over the right DLPFC, cathodal electrode over the left occipital cortex) increased cue-induced brain activity of the right posterior cingulate cortex in comparison to sham. There was also a significant reduction in craving. However, there were no significant differences in the amount of tobacco smoking or exhaled carbon monoxide. Thus, these results suggest that using a unilateral montage to target the DLPFC might not be optimal.

Delivering tDCS over the bilateral DLPFC appears to hold more promise compared to other montages, at least in SUDs (Ekhtiari et al. 2019; Jansen et al. 2013). This is because it has decreased craving and drug consumption. As previously discussed, craving is a very important predictor of relapse. Following this logic, targeting the bilateral DLPFC could decrease craving and help patients maintain abstinence in GD. All studies investigating tDCS-induced effects on functional connectivity and neurochemistry have targeted both DLPFCs.

A few sham-controlled RCTs evaluated tDCS-induced effects on rs-FC in patients with SUDs, comparing before and after stimulation. One study found that a single

session of tDCS increased rs-FC between the left DLPFC seed (under the anode) and the right parahippocampal gyrus in patients with Tobacco Use Disorder, which was negatively correlated with reductions in craving (Yang et al. 2017). Another study showed that one tDCS session modulated rs-FC of 3 networks in patients with Methamphetamine Use Disorder (Shahbabaie et al. 2018). More specifically, tDCS deceased rs-FC of a default mode network and increased rs-FC of an executive control network and a salience network. These changes were also correlated with reductions in craving.

Furthermore, one study found that 5 daily sessions of tDCS modulated graph theoretical metrics of the entire brain (i.e., increased global efficiency, reduced clustering) and increased functional connectivity of a right frontal network in patients with Alcohol Use Disorder (Holla et al. 2020). Also, increased global efficiency predicted a lower chance of relapsing. In addition, the change in global clustering was positively correlated with reduced impulsivity level (Stop Signal Reaction Time Task). Thus, it appears that targeting the bilateral DLPFC may be clinically relevant for patients with SRADs, and possibly GD.

To our knowledge, no published studies assessed the effects of tDCS on neurochemistry in patients with SUDs. One sham-controlled study assessed neurochemistry in GD patients (Dickler et al. 2018). In this work, tDCS was delivered over the bilateral DLPFC (anode over the right and cathode over the left DLPFC, respectively). Glx and GABA levels were compared between active and sham tDCS during tDCS stimulation. Active tDCS significantly increased GABA levels in the right DLPFC. Furthermore, positive correlations were reported between increased metabolite levels during stimulation and baseline symptoms. More specifically, greater risk-taking (scores on the Balloon Analog Risk Task-BART) was positively correlated with higher Glx levels measured during active tDCS in the right DLPFC and the right striatum. The BART is a computerized task that measures risk-taking (Lejuez et al. 2002). It is associated with real-life risky behaviours, such as substance use (Lejuez et al. 2005) and unsafe sexual activity (Lejuez et al. 2004). Participants

are asked to inflate a virtual balloon using a pump. They are rewarded money during each pump, which accumulates in a temporary bank. However, with each pump, there is increasing risk of explosion. If the balloon explodes, the participant loses all the money in the temporary bank for that trial. If they successfully decide to stop pumping, the accumulated money is transferred to a permanent bank. The most popular unit of measure is the average number of pumps on balloons that did not explode (i.e., the mean number of pumps prior to collecting money).

In addition, higher impulsivity (scores on the Barratt Impulsiveness Scale-BIS) was positively correlated with larger n-acetyl-aspartate level measured during active tDCS in the right striatum. Further, larger craving was positively correlated with Glx levels measured during active tDCS in the right striatum. These findings suggest that patients with more severe symptoms might respond better to tDCS, which might help identify best responders. Importantly, this study showed that we can use tDCS to modulate GABA levels in neural circuits relevant to GD, which is an important step in the right direction.

Altogether, studies have showed that tDCS can target function and neurochemistry in patients with SRADs. More specifically, targeting the bilateral DLPFCs can modulate rs-FC in networks relevant to GD. Some of these changes have also been associated with reduced craving. These findings not only provide a mechanistic result, but also an important clinical meaningful one; meaning that it can alleviate symptoms in patients. Thus, one could suppose that tDCS targeting the DLPFC might also potentially modulate functional connectivity and alleviate symptoms such as craving in patients with GD.

1.2.3 tDCS in gambling disorder: potential to modulate substrates and treat patients?

It is only since 2018 that tDCS has been studied in patients with GD. Four sham-controlled studies assessed the clinical effects of tDCS in patients with GD. The first was a case study in a male patient with GD (Martinotti et al. 2018). He received 2

daily sessions over 10 days targeting the DLPFC (first session: anode over the left DLPFC, cathode over the right DLPFC; second session: reverse montage). After 10 days, the patient displayed several improvements in symptoms, including decreased craving, GD severity, anxiety, depression, and impulsivity as compared to sham. Remarkably, the patient also stopped gambling. All symptom improvements lasted at 3- and 6-month follow-ups. However, one must exert caution as case studies have several limitations such as publication bias and the impossibility to generalize (Nissen and Wynn 2014).

The second study was a sham-controlled study that assessed whether tDCS could improve cognitive control in 20 patients with GD (Soyata et al. 2019). tDCS was delivered over the bilateral DLPFC (anode over the right DLPFC, cathode over the left DLPFC) over 3 tDCS sessions. Cognitive processes were assessed before and after the tDCS regimen. More specifically, the authors measured decision-making and cognitive flexibility, using the Iowa Gambling Task and Wisconsin Card Sorting Test, respectively. Patients that received active stimulation displayed better decision-making (increased net scores on the Iowa Gambling Task) and cognitive flexibility (reduced perseveration errors on the Wisconsin Card Sorting Test) as compared to sham.

Furthermore, in the third study, daily tDCS sessions over five days (anode over the right DLPFC, cathode over the left DLPFC) decreased craving in poly-users (including two patients with GD) (Martinotti et al. 2019). Lastly, a recent case report found that six sessions of tDCS (anodal over the right DLPFC, cathodal over the left DLPFC) over ten days decreased impulsivity (Go/No-Go task) and risk-taking (BART) in a male patient with GD, although the improvement in risk-taking was not significant at the 2-week follow-up period (Salatino et al. 2021). There were also some clinical improvements at follow-up, such as improved cognitive functioning and reduced GD severity. However, symptoms of anxiety worsened at follow-up, supporting the importance of monitoring long-term symptoms in general.

Taken together, clinical studies support tDCS as a potential treatment for GD. However, larger RCTs are needed to investigate clinical efficacy.

1.3 General objectives and hypotheses of this thesis

As discussed in previous sections, current treatments for GD have limited effectiveness. This could be due to various factors, such as not being specific enough to symptoms. A better characterisation of the neural substrates of GD will likely contribute to develop treatments that are more specific for them. It is only recently that the neural substrates of GD have been investigated, thus knowledge remains limited, and more work is needed. Non-invasive neuromodulation techniques, such as tDCS, hold promise to treat GD. As such, tDCS allows to target neural substrates, is safe and has minimal side effects.

In addition, tDCS has shown promise in several RCTs to decrease symptoms important for relapse (e.g., craving) in SUDs (Ekhtiari et al. 2019). Since GD is purported to share neural substrates and symptoms (e.g., craving and cognitive symptoms) with SUDs, one could propose that tDCS might also help treat patients with GD. Additionally, tDCS can improve symptoms, i.e., reducing craving, strengthening cognitive control (Martinotti et al. 2018; Martinotti et al. 2019; Soyata et al. 2019; Salatino et al. 2021) and modulate neurochemical levels (Dickler et al. 2018) in patients with GD. This supports even more the clinical potential of tDCS to treat patients with GD.

Therefore, the main objectives of this thesis are two-fold: 1) to better understand the neural substrates of GD; 2) to examine tDCS-induced effects on substrates in patients with GD. It also seems important to determine whether morphometry of the stimulation site (DLPFC) can influence tDCS-induced effects on substrates, since patients with GD frequently present morphometric differences as compared to healthy individuals. Hence, the other objective of this thesis is to explore whether morphometry of the DLPFC influences tDCS-induced effects on substrates (rs-FC and neurochemistry) in patients with GD. The main hypotheses of this thesis are

that: 1) patients with GD will display morphometric and functional signatures that are related to the clinical profile; 2) tDCS will modulate neural substrates that may be clinically relevant for GD, which will support its use as a future therapeutic tool. Further, the other hypothesis was that greater morphometry of the DLPFC will be associated with greater tDCS-induced effects on rs-FC and neurochemistry. In sum, the results of this thesis will contribute to the knowledge of not only GD, but other disorders that share neural substrates such as SUDs and other non-substance-related disorders (e.g., internet gaming disorder).

Chapter 2: Brain morphometry in adults with gambling disorder

Résumé

Introduction : Il y a plusieurs inconnues à propos des substrats neuronaux du trouble du jeu de hasard et d'argent, incluant la morphométrie cérébrale à base de surface et les liens de celle-ci avec le profil clinique. Une meilleure compréhension des substrats neuronaux est importante pour établir de nouvelles cibles pour traiter les patients avec trouble du jeu de hasard et d'argent.

Objectifs : Le but de cette étude était d'examiner la morphométrie à base de surface chez les patients avec trouble du jeu de hasard et d'argent en comparant leurs structures cérébrales à une base de données normative d'individus en santé et d'explorer la signification clinique de leurs structures.

Méthode : Nous avons mesuré l'épaisseur, la superficie et le volume du cortex ainsi que le volume sous-cortical. On a comparé ces mesures à celles d'une base de données normative en contrôlant pour plusieurs facteurs tels que l'âge et le sexe. On a aussi testé pour des corrélations avec des facteurs reliés au trouble du jeu de hasard et d'argent, c'est-à-dire, la sévérité et la durée du trouble du jeu de hasard et d'argent, l'impulsivité et les symptômes dépressifs (mesuré avec le « South Oaks Gambling Screen », années du trouble du jeu de hasard et d'argent, « Barratt Impulsiveness Scale » et le « Beck Depression Inventory »).

Résultats : Comparés à la base de données normative, les patients avec trouble du jeu de hasard et d'argent ont un cortex préfrontal et pariétal plus mince et un cortex occipital et entorhinal plus épais et volumineux. De plus, les régions sous-corticales avaient un volume plus élevé. Nous avons identifié deux corrélations positives entre la superficie du cortex occipital et les symptômes dépressifs.

Conclusions : Ce travail contribue à mieux comprendre les substrats neuronaux du trouble du jeu de hasard et d'argent. Ces substrats neuronaux ressemblent à ceux

des troubles liés aux substances ainsi que le l'usage pathologique des jeux sur internet. Finalement, nos résultats suggèrent que les substrats ne doivent pas nécessairement être différents des normes des individus en santé pour être cliniquement significatifs.

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Title: Brain morphometry in adults with gambling disorder

Running title: Gambling brain morphometry

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Abstract

Little is known regarding the brain substrates of Gambling Disorder, including surface brain morphometry, and whether these are linked to the clinical profile. A better understanding of the brain substrates will likely help determine targets to treat patients. Hence, the aim of this study was two-fold, that is to examine surface-based morphometry in patients with gambling disorder as compared to norms of healthy individuals and to assess the clinical relevance of morphometry in patients with Gambling Disorder. This study measured brain volume, surface and thickness in Gambling Disorder. We compared these measures to those of a normative database that controlled for factors such as age and sex. We also tested for correlations with gambling-related behaviors, such as gambling severity and duration, impulsivity, and depressive symptoms (assessed using the South Oaks Gambling Screen, years of gambling, Barratt Impulsiveness Scale, and Beck Depression Inventory, respectively). Patients displayed thinner prefrontal and parietal cortices, greater volume and thickness of the occipital and the entorhinal cortices, and greater volume of subcortical regions as compared to the norms of healthy individuals. There were positive correlations between surface area of occipital regions and depressive symptoms. This work contributes to better characterize the brain substrates of Gambling Disorder, which appear to resemble those of substance use disorders and Internet Gaming Disorder. Finally, these findings underscore that substrates may not have to be different from norms of healthy individuals to carry clinical significance.

Keywords
Gambling Disorder, occipital cortex, surface-based morphometry

1. Introduction

Gambling Disorder (GD) is defined as a persistent and recurrent maladaptive behavior that leads to a repetitive loss of control over both time and money spent gambling and can lead to negative consequences (e.g., poor quality of life) (American Psychiatric Association, 2013). Although cognitive-behavioral treatments show some promise to treat patients, relapse and attrition remain high. For example, 77% of patients relapse after 12 months (Hodgins et al., 2007) and attrition rates vary between 14% and 50%, with a median 26% dropout rate (Melville et al., 2007). Patients with GD can also display cognitive deficits which may influence treatment outcomes (Grant et al., 2016). As a possible complement to cognitive-behavioral treatments in order to increase treatment adherence, Challet-Bouju et al. (Challet-Bouju et al., 2017) advocate for a set of interventions that target neuroplasticity, focusing on cognitive processes such as impulsivity, in parallel with the content of thoughts. Targeting mood might also be of interest, considering that almost 40% of patients with GD display depressive disorders (Potenza et al., 2019). A better understanding of links between clinical measures and brain substrates in GD will likely contribute to identify key regions that may be important to target with treatments.

To our knowledge, eight studies found differences in brain volume in GD as compared to healthy controls (Koehler et al., 2015; Mohammadi et al., 2016; Rahman et al., 2014; Ruiz de Lara et al., 2018; Takeuchi et al., 2019; Takeuchi et al., 2017; van Holst et al., 2012; Zois et al., 2017). There does not appear to be a consensus regarding findings across these studies, possibly due to the differing methods used (hence it is difficult to compare results across studies). One such method is surface-based morphometry, which allows to measure volume, as well as cortical surface area and thickness. Surface area and thickness may be particularly interesting to investigate, since they have different underlying mechanisms during cortical development (Rakic, 1988), are uncorrelated genetically (Panizzon et al., 2009) and differ during healthy aging (Hogstrom et al., 2013). Three studies

assessed morphometry in GD as compared to healthy controls using surface-based methods with FreeSurfer (Fuentes et al., 2015; Grant et al., 2015; Rahman et al., 2014). Grant et al. (2015) investigated cortical thickness (Grant et al., 2015) and found eight clusters of cortical thinning, located in frontal (right superior frontal, rostral middle frontal, medial orbitofrontal cortices) and parietal regions (right supramarginal gyrus, right postcentral gyrus, and left inferior parietal cortex). They also studied volume of subcortical regions of interest (ROIs) (putamen, caudate, accumbens, hippocampus, amygdala), but found no significant differences for these measures. Fuentes et al. (2015) conducted whole-brain voxel-wise comparisons (Fuentes et al., 2015) and found no significant differences. They also tested ROIs of the fronto-striatal circuit and medial temporal regions and found smaller volumes of the left putamen, right hippocampus and right thalamus (uncorrected for multiple comparisons). Rahman et al. (2014) examined two ROIs (Rahman et al., 2014), the amygdala and hippocampus, and found smaller volume of the right amygdala and left hippocampus.

These three surface-based morphometry studies (Fuentes et al., 2015; Grant et al., 2015; Rahman et al., 2014) explored for potential correlates with behaviors. However, none of them reported significant correlations (when corrections for multiple corrections were applied). In Grant et al. (2015), cortical thicknesses found to be different from the healthy control group did not significantly correlate with severity of GD (Grant et al., 2015). In Fuentes et al. (2015), there were no correlations between volumes of the ROIs and severity of GD (Fuentes et al., 2015). In Rahman et al. (2014), there was a trend indicating a positive correlation between volume of the left amygdala and impulsivity level that however did not survive Bonferroni corrections (Rahman et al., 2014). In sum, there is a need to investigate brain morphometric differences in GD, since brain differences remain unclear across studies and there are no definitive answers as to which substrates carry clinical significance.

Thus, the goal of this work was to investigate brain morphometry in GD. Specifically, the first aim was to characterize cortical volume, thickness, and surface, as well as volume of subcortical structures in adults with GD using a data-driven approach as compared to a normative database of healthy individuals (Potvin et al., 2017; Potvin et al., 2016). We hypothesized that patients with GD will display thinner prefrontal and parietal cortices (Grant et al., 2015). In regard to subcortical regions, one study reported smaller right amygdala and left hippocampus (Rahman et al., 2014), whereas one study found no significant differences (Fuentes et al., 2015), we thus did not emit predictions but our work will contribute to this line of work. The second aim was to identify the clinical relevance of brain morphometric measures in GD. Most previous work indicated non-significant correlations using ROIs, thus here we studied correlations between clinical characteristics and morphometric measures using a whole brain approach (cortical volume, thickness, and surface, as well as volume of subcortical regions). We postulated that there might be a positive correlation between volume of the left amygdala and impulsivity levels as assessed by the Barratt Impulsiveness Scale (BIS) (Rahman et al., 2014). We also explored for potential clinical correlates of severity of gambling with the South Oaks Gambling Screen (SOGS), duration of gambling, and depressive symptoms with the Beck Depression Inventory (BDI).

2. Materials and Methods

2.1 Patients

We recruited eighteen adults meeting DSM-5 criteria for GD. They were selected with strict selection criteria (i.e., no medical conditions, neurological disorders (including possible traumatic brain injury), psychiatric conditions (other than depressive and anxiety symptoms), and no substance use disorders in the last year (other than tobacco use disorder)). We used G*Power to calculate the sample size (Faul et al., 2007). We calculated that a sample of 17 participants would be needed to detect a large effect size (Cohen's d = 1) with 85% power and an α of .01, for a two-tailed, one-sample t-test. A one-sample t-test was used since the norm has a z-

score of zero and morphometric differences are displayed as z-score differences from the norm. We considered a 2.7% drop-out rate, based on a previous surface-based structural imaging study that reported withdrawal of 1/37 participants due to MR-related anxiety (Fuentes et al., 2015), thus requiring 18 participants. One participant was excluded due to structural MRI artefacts. We thus report data of seventeen adults (mean age = 41.2 years, SD = 16.7; eight women; five left-handed; mean years of education = 13.3, SD = 1.7). Participants provided their written informed consent prior to their participation and were screened for their eligibility to undergo MRI scanning. This study received ethics approval from the local committee.

2.2 Behavioral assessment of patients with gambling disorder

Patients were assessed on gambling severity in the past year with the SOGS (Strong et al., 2004) (mean score = 10.1, SD = 3.8) and had a mean duration of gambling of 7.4 years (SD = 8.1). They were also assessed on the BIS-10 (Patton et al., 1995) (mean score on the full scale = 68.7, SD = 12.8), and on the BDI (Beck et al., 1961) (mean score = 17.9, SD = 9.9). To note, data was missing for one patient for the SOGS, BIS and BDI, thus correlations were conducted with sixteen adults for these measures.

2.3 MRI data acquisition and preprocessing

Patients were scanned using a Philips 8-channel SENSE Head coil 3 Tesla Achieva scanner (Philips Healthcare, Best, The Netherlands). We acquired T1-weighted structural magnetic images with a magnetization prepared rapid acquisition gradient-echo sequence (repetition time = 8.2 ms; echo time = 3.7 ms; field of view = 250 mm; flip angle = 8º; 256 x 256 matrix; 180 slices/volume; slice thickness = 1 mm; no gap). We used the computing platform of CBrain (Sherif et al., 2014) to run FreeSurfer's recon-all pipeline with default parameters (https://surfer.nmr.mgh.harvard.edu). Since the normative database tool uses version 5.3.0 of FreeSurfer, we used this version for aim 1. We used the latest version of FreeSurfer (version 6.0.0) for aim 2, since it provided technical

improvements and potentially a more precise estimate of cortical volume (https://surfer.nmr.mgh.harvard.edu/fswiki/ReleaseNotes; (Winkler et al., 2018)). We parcellated the cortex with the Desikan-Killiany-Tourville atlas (Klein and Tourville, 2012), the perirhinal (Augustinack et al., 2013) and entorhinal (Fischl et al., 2009) cortices with the ex vivo protocol, and segmented the subcortical regions with FreeSurfer's aseg atlas (Fischl et al., 2002).

2.4 Data and statistical analyses

For aim 1, that is to identify potential differences between GD and the norms of healthy individuals, we used a normative database tool (https://github.com/medicslab/mNormsFS53) to compare matched healthy controls to patients' structural data. This is an automated tool that allows to measure how one's brain structure deviates from the norm. The rationale behind the creation and use of this normative database is two-fold. Firstly, there was a need for adequate and reliable neuroanatomic reference standards (Potvin et al., 2016). Secondly, measuring brain morphometry at the individual level could be problematic since no specific reference exists as to how much one's morphometry deviates from the norm according to specific characteristics (age, sex, etc.) (Potvin et al., 2016). The database was created by collecting 2713 cortical and 2790 subcortical anatomical scans from healthy individuals from 23 samples of 21 independent research groups across the world. Scans were processed using FreeSurfer 5.3.0. After, the authors created linear regression models for cortical (Potvin et al., 2017) and subcortical regions (Potvin et al., 2016) which were validated in an independent sample of healthy individuals, demonstrating satisfactory R^2 values for each brain region. The database controls for several factors, i.e., age, sex, estimated total intracranial volume, as well as MR scanner manufacturer and field strength. The use of this normative database offers the advantage of validated population norms that can detect differences between neuropsychiatric populations and healthy individuals, thus reducing the need to enroll healthy participants. Differences between patients and healthy controls are displayed as z-scores, where the mean (i.e., norm) has a z-score of zero. Patient z-scores are represented as scores deviating from the norm.

We entered resulting patient Z-scores into a series of one-sample t-tests, in which the reference value was equal to zero. The resulting t values indicated the strength and direction of the differences in volume, thickness and surface between GD and the norms of healthy individuals. We used Glass's Δ to assess effect sizes. For aim 2, that is to test for correlations between brain morphometry and patient characteristics, we entered morphometric data (volume, thickness, surface) and scores from the SOGS, BIS, BDI, and years of gambling into Pearson's r correlation tests, controlling for age and estimated total intracranial volume. Statistical significance was set at $p < .01$ for aim 1 and $p < .05$ for aim 2 since it was exploratory.

When appropriate, we performed post-hoc comparisons using Bonferroni correction for the total number of brain regions within a morphometric measure: regional cortical volume, thickness, and surface (threshold of $\alpha = .01/64$ regions = .00016, each), regional subcortical volume ($\alpha = .01/17$ regions = .00059), total volume (i.e., total subcortical volume, total cortical volume of the left hemisphere, total cortical volume of the right hemisphere; $\alpha = .01/3$ regions = .0033), as well as total surface and thickness ($\alpha = .01/2$ regions = .005, each). Analyses were performed using IBM® SPSS® Statistics, version 26 (SPSS Inc., Chicago, Illinois, U.S.A.).

3. Results

3.1 Brain morphometry differences between patients with gambling disorder and the norms of healthy individuals

There were significant morphometric differences between patients with GD and the norms of healthy individuals, (please refer to Table 1 for all significant statistical values). In the frontal cortex, patients with GD displayed thinner caudal and rostral middle frontal gyri and thinner superior frontal gyrus of the left hemisphere (Figure 1). In the parietal cortex, they showed thinner inferior parietal gyrus of the right hemisphere. In the occipital cortex, they had greater volume and thickness of both pericalcarine cortices. Further, they showed greater volume and thickness of the left lingual gyrus, as well as thicker right lingual gyrus. In the temporal cortex, they had

thicker and greater volume of both entorhinal cortices. There were no significant differences of surface. For the subcortical areas, all differences were in the same direction (Figure 2), that is patients had greater volume of both pallida, both putamina, both thalami proper, the right nucleus accumbens, the right ventral diencephalon, and the right caudate nucleus, as well as of the total subcortical gray matter.

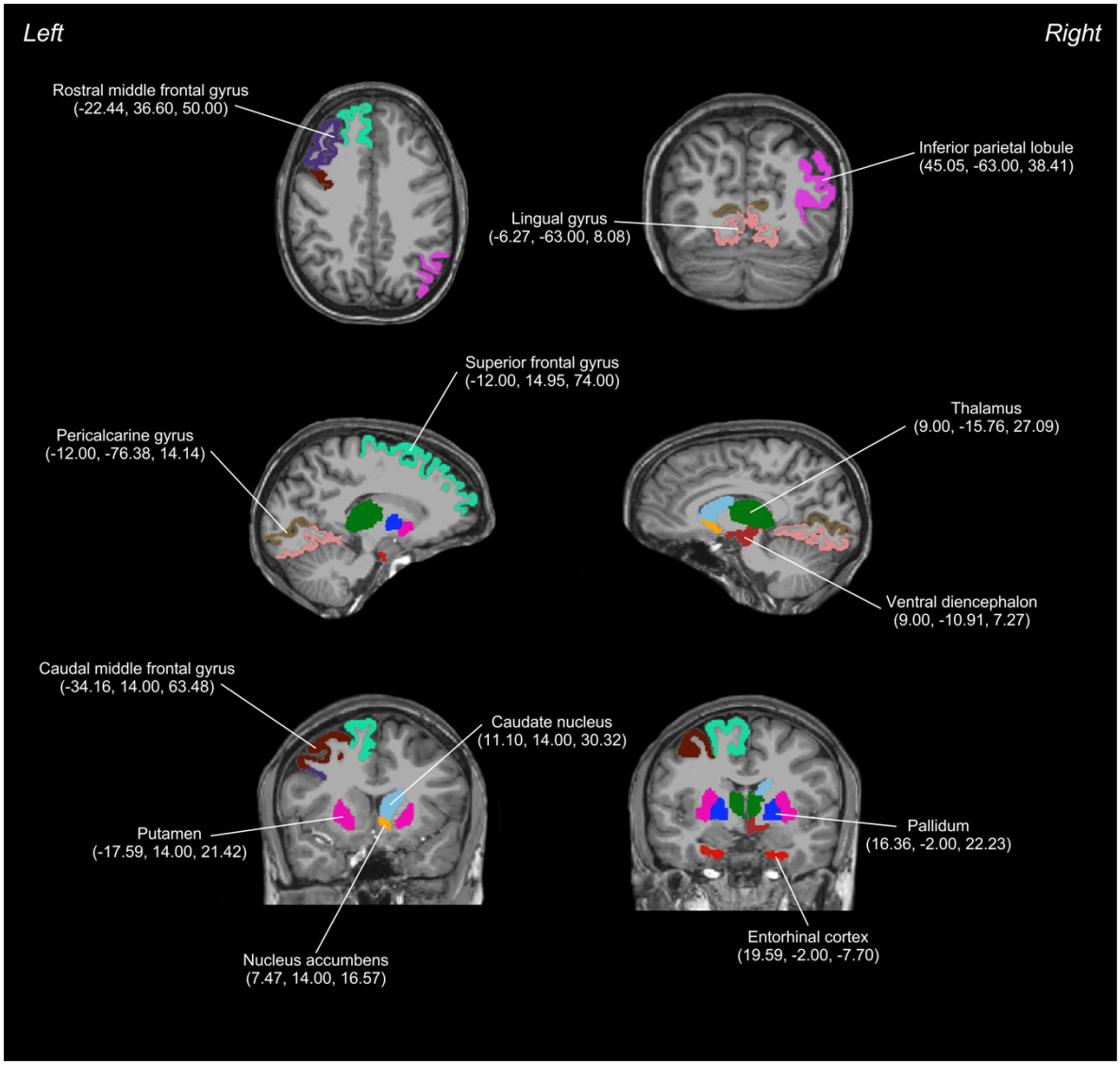
Table 1. Cortical morphometric measures that are different between patients with gambling disorder and the norms, corrected for multiple comparisons.

	Descriptive statistics[a]		Normative transformation		One sample T-test	
	Mean	SD	Z-score (Glass' Δ)	SD	T-score (from 0)	P value
Volume						
Occipital lobe						
L lingual	7166.82	913.99	1.25	1.01	5.07	<.001
R pericalcarine	2509.00	462.48	1.19	.98	5.00	<.001
L pericalcarine	2329.47	518.67	1.18	.97	5.01	<.001
Temporal lobe (medial)						
R entorhinal cortex (ex vivo)	1092.53	358.81	1.33	.91	6.01	<.0001
L entorhinal cortex (ex vivo)	1900.82	534.04	1.31	1.02	5.32	<.0001
Subcortical regions						
R caudate nucleus	3815.13	574.11	1.45	1.05	5.69	<.0001
R nucleus accumbens	634.79	128.48	1.44	.87	6.86	<.00001
R pallidum	1891.48	244.64	2.07	1.14	7.49	<.00001
L pallidum	2001.10	311.40	1.94	.86	9.33	<.0000001
R putamen	5069.96	739.96	1.37	1.08	5.22	<.0001
L putamen	5186.73	752.39	1.66	1.19	5.73	<.0001
R thalamus proper[b]	7905.00	740.95	1.27	1.03	5.08	<.001
L thalamus proper[b]	8259.02	841.36	.81	.56	5.97	<.0001
R ventral diencephalon[c]	4200.51	374.16	1.26	1.17	4.45	<.001

Total subcortical gray matter	61316.94	5675.80	2.23	1.13	8.14	<.000001
Thickness						
Frontal lobe						
L caudal middle frontal gyrus	2.30	.11	-1.33	.79	-6.97	<.00001
L rostral middle frontal gyrus	2.20	.12	-1.29	.87	-6.11	<.0001
L superior frontal gyrus	2.39	.14	-1.69	.89	-7.84	<.000001
Occipital lobe						
R lingual gyrus	2.12	.13	1.25	.89	5.78	<.0001
L lingual gyrus	2.11	.12	1.52	.82	7.61	<.00001
R pericalcarine cortex	1.78	.14	1.33	.91	6.01	<.0001
L pericalcarine cortex	1.71	.16	1.09	.85	5.33	<.0001
Parietal lobe						
R inferior parietal lobule	2.25	.11	-1.20	.92	-5.34	<.0001
Temporal lobe (medial)						
R entorhinal cortex (ex vivo)	3.27	.43	1.20	.65	7.62	<.00001
L entorhinal cortex (ex vivo)	3.14	.29	1.23	.99	5.15	<.0001

L: left hemisphere; R: right hemisphere; SD: standard deviation.
[a]Thickness in mm and volume in mm^3; descriptive statistics are calculated from FreeSurfer version 6.0.0
[b]Thalamus proper includes all thalamic nuclei except the lateral and medial geniculate bodies.
[c]Ventral diencephalon includes the basal forebrain, hypothalamus, sublenticular extended amygdala, and a great part of the ventral tegmentum

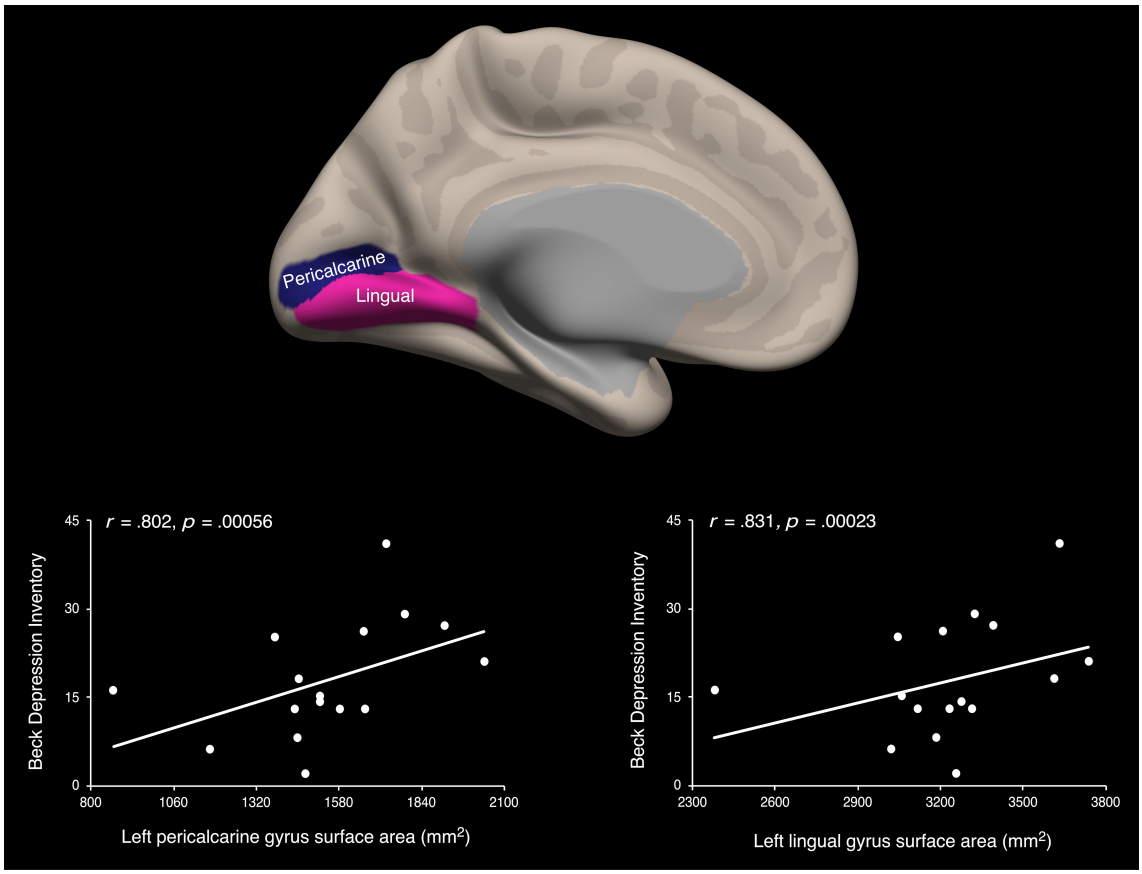
Figure 1. Cortical and subcortical regions that are different between patients with gambling disorder and the norms, corrected for multiple comparisons (p < .01; Bonferroni corrections were applied for the number of regions within a measure: regional cortical volume, thickness, and surface (α threshold = .01/64 regions, = .00016), regional subcortical volume (α = .01/17 regions = .00059), total volume (subcortical, cortical of the left hemisphere, cortical of the right hemisphere; α = .01/3 regions = .0033), and total surface and thickness (α = .01/2 regions = .005). Regions are depicted by different colors (i.e., identical colors correspond to identical regions) and RAS (right, anterior, superior) coordinates from FreeSurfer.



3.2 Correlation between brain morphometric and behavioral measures

There were positive correlations between the BDI scores and surface of occipital regions, that is the left lingual (r = .831, p = .00023) and the left pericalcarine gyri (r = .802, p = .00056) (Figure 3). There were no significant correlations between morphometric measures and gambling severity (SOGS scores), gambling duration, or impulsivity (BIS scores) that survived Bonferroni corrections.

Figure 2. Correlations between morphometric measures and behavioral outcomes, corrected for multiple comparisons ($p < .05$, α threshold = .00078).



4. Discussion

The goal of this study was to assess potential brain morphometric differences between adults with GD and the norms of healthy individuals and whether morphometric substrates carry clinical relevance in GD. Overall, patients displayed

frontal and parietal cortical thinning, greater volume and thickness of the occipital and temporal cortex, as well as greater volume of subcortical areas. Patients displayed positive correlations between occipital surface area and depressive symptoms.

Results indicate that the prefrontal and parietal cortices were thinner in GD as compared to the norms, which is in line with previous work. In the frontal cortex, differences were all in the same direction, that is patients had thinner structures and they were all found in the left hemisphere. Thinner prefrontal regions have also been previously found, but in the right hemisphere (Grant et al., 2015). In our study, there were other thinner regions in both hemispheres that however did not survive after correction for multiple comparisons (Table S1). Thinner frontal regions might not be specific to GD as they have been observed in substance dependent populations (encompassing alcohol, nicotine, cocaine, methamphetamine, cannabis), especially in the left caudal middle frontal gyrus and the right medial orbitofrontal cortex (Mackey et al., 2019), as well as in video game players in the ventromedial, dorsomedial, dorsolateral prefrontal cortices, and superior frontal gyri (He et al., 2020). In the parietal cortex, patients displayed a thinner right inferior parietal lobule. Thinner parietal regions have been reported in GD ((Grant et al., 2015), left inferior parietal cortex, right supramarginal gyrus and right post-central gyrus), video game players ((He et al., 2020), left superior parietal lobe) and across substance use disorders ((Mackey et al., 2019), left inferior parietal, bilateral paracentral, left precuneus, left superior parietal, bilateral supramarginal cortices). Overall, it seems that frontal and parietal substrates resemble those of substance use disorders and video gaming.

Interestingly, differences in the occipital cortex were all in the same direction, that is patients had greater thickness and volumes of bilateral pericalcarine cortex, left lingual gyrus, as well as thicker right lingual gyrus. Further, the surface area of the left pericalcarine and lingual gyri positively correlated with severity of depressive symptoms as assessed by the BDI. Almost 40% of patients with GD are estimated

to have depressive symptoms (Potenza et al., 2019), which was represented in our patient sample. About 60% of our patients displayed depressive symptoms as assessed by the BDI. It might be interesting for future studies to assess the importance of the left pericalcarine and lingual gyri in major depressive disorder and GD. A strong significance might promote the measurement of these regions as biomarkers for disorder severity. Interestingly, there is another line of work indicating positive correlations between occipital volume and thickness and addictive-related behaviors. For instance, volume of a left occipital/inferior parietal cluster positively correlated with duration of video gaming (Kühn and Gallinat, 2014) and larger volumes of the bilateral middle occipital gyrus and left inferior occipital gyrus were associated with greater alcohol consumption in healthy individuals (Sachdev et al., 2008). These suggest that occipital morphometry presumably changes with the load of addictive behaviors (duration of video game, alcohol consumption) and may involve visual attention to salient stimuli. Indeed, patients with Substance-Related and Addictive Disorders are known to show attentional biases towards addiction related stimuli (e.g., gambling cues (Anselme and Robinson, 2020; Vizcaino et al., 2013)). In regard to other Substance-Related and Addictive Disorders, previous studies have reported inconsistent results. Some observed greater volume of the occipital cortex in patients with tobacco use disorder (right lingual gyrus) (Zhong et al., 2016) and thicker occipital cortex in patients with stimulant use disorder (Li et al., 2014), whereas others found smaller volumes of the occipital cortex in alcohol (Wang et al., 2018), cannabis (Hill et al., 2016), and cocaine use disorders (Meade et al., 2020). Overall, it appears that the occipital substrates in GD largely resemble those of video gaming, as well as possibly methamphetamine use disorder.

In the entorhinal cortex, differences were all in the same direction, that is patients had greater volume and thicker cortices in both hemispheres. This supports previous work indicating greater volume of medial temporal regions in patients with Internet Gaming Disorder (Yoon et al., 2017). Also, volume of the entorhinal cortex positively correlated with duration of video gaming in players (Kühn and Gallinat, 2014). There seems to be not much on the entorhinal cortex in substance use disorders and the

existing data appear to indicate smaller or thinner regions, including thinner parahippocampal gyrus in alcohol use disorder (Mackey et al., 2019), and smaller volume of the parahippocampal gyrus in methamphetamine-induced psychotic disorder (Farnia et al., 2020) and in cocaine use disorder (Moreno-López et al., 2012). It seems that patients with GD may share entorhinal substrates with gaming disorders.

In subcortical areas, differences were all in the same direction, that is patients displayed greater volume of structures than the norms of healthy individuals. We found greater volume of the striatum (nucleus accumbens, putamina, pallida, and caudate nucleus). Greater striatal volume has been previously reported in GD (Koehler et al., 2015), as well as in Internet Gaming Disorder (Yuan et al., 2017). Interestingly, this seemingly contrasts with findings in substance use disorders, since smaller volume of the nucleus accumbens has been reported (Mackey et al., 2019). This might reflect that GD and substance use disorders differ in regard to subcortical processing. We also found greater volume of the thalamus, which has also been found in Internet Gaming Disorder (Han et al., 2012). Further, we found a larger volume of the ventral diencephalon (sublenticular extended amygdala, the hypothalamus, basal forebrain and part of the ventral tegmentum). It seems that subcortical volume of patients with GD resemble substrates mainly of Internet Gaming Disorder. Interestingly, we observed thinner frontal regions and greater volume of subcortical regions, which raise the question as to whether there is little top-down control or overly strong bottom-up processing, as previously discussed (Koehler et al., 2015).

There were no differences of surface area, but of thickness and volume. Surface area is thought to represent the number of cortical columns, whereas thickness is thought to represent the number of neurons within a cortical column (Rakic, 1988). Differences in volume could reflect differences in thickness and/or surface area, since volume is calculated as a product of these two measures. As such, it seems that differences in thickness and surface area occur differently from each other, since

they are genetically uncorrelated, which could reflect two different underlying mechanisms (Panizzon et al., 2009). Indeed, some suggest that they should be considered as two separate entities (Panizzon et al., 2009; Storsve et al., 2014). For example, a cross-sectional study in healthy individuals found a negative correlation between surface area and thickness (Hogstrom et al., 2013). Also, a longitudinal study by Storsve et al. (2014) investigated the relationship between morphometric changes over 3.6 years in healthy individuals (Storsve et al., 2014). They found both negative correlations between surface area and thickness, where larger decreases in thickness were related to smaller reductions in surface area. Volume appeared to be closely related to changes in thickness as compared to surface area, since there were positive correlations with thickness and there were mixed (both negative and positive) correlations with surface area. This seems to be in line with our results, since structures that differed in both thickness and volume did so in identical directions (i.e., both greater thickness and volume). It appears in our study that the differences in volume are mediated by the differences in thickness but not surface area. It has been proposed that differences in thickness, but not surface area, reflect a change in the number of neurons but not a difference in the organization of columns or brain size (Hibar et al., 2018). Thus, GD may display smaller or greater number of neurons in certain brain regions, whereas the number of columns remains the same. Regarding volume, preclinical work has shown that it is related to dendritic spine density (Keifer et al., 2015), possibly reflecting greater afferent connectivity. Also, greater thickness was correlated with bigger total dendritic length in human brain slices (Goriounova et al., 2018). Thus, one may speculate that larger volume and thickness may reflect greater connectivity as compared to regions with smaller volume or thickness. In patients, it seems that the number of cortical columns is associated with clinical and behavioral correlates, but not the number of neurons in these columns. This highlights the pertinence of testing for correlations between morphometry and correlates, independently of any differences, in order to better understand the substrates of GD. Furthermore, there was no relationship between impulsivity and amygdala volume ($p > .48$), which is opposite to the finding by Rahman et al. (2014) (Rahman et al., 2014). This might reflect differences between

the two samples, as well as differences between methods and analyses. For instance, patients in their study displayed normal anxiety and depression levels. Although we did not measure anxiety levels in our patients, they displayed borderline clinical depression. This appears to be in line with characteristics of the population, in which about 40 % can display mood disorders and more than 50 % can have anxiety disorders (Potenza et al., 2019). Future work should test for relationships between limbic volume and impulsivity level in patients with varying mood disorders. We compared brain morphometry of patients with GD was to that of healthy individuals using a normative database. This database is advantageous since it provides validated normative data that allows to determine deviation from the norm controlling for several factors such as age and brain size. However, the database does not control for demographic data (e.g., years of education or handedness), which may influence morphometry (Boller et al., 2017; Hatta, 2007). Nevertheless, using this tool may offer complementary findings to previous work, considering that these studies compared morphometry to cohorts of healthy individuals and there are mixed findings (Koehler et al., 2015; Mohammadi et al., 2016; Rahman et al., 2014; Ruiz de Lara et al., 2018; Takeuchi et al., 2019; Takeuchi et al., 2017; van Holst et al., 2012; Zois et al., 2017).

4.1 Limitations and future directions

This study is not without limitations. Firstly, it is unclear whether our results reflect a predisposition and/or a consequence of GD, due to the cross-sectional nature of this study. Secondly, our patients were treatment-seekers, and it is estimated that a large majority of patients with GD do not seek treatment (i.e., about 10% seek treatment (Potenza et al., 2019)), thus the sample studied here may not be representative of the entire GD population. Further, it is unclear as to which extent comorbidities contributed to our results. As such, half of our sample were tobacco smokers, 60% had depressive symptoms, and two patients had a history of other substance use disorders (but were abstinent for at least one year prior to their participation). Yet, it seems pertinent to assess brain morphometry in a sample that is representative of the actual GD population (Potenza et al., 2019). It is therefore of interest to study a

population with GD and comorbidities to better understand the substrates of the disorder to develop better treatment strategies. Indeed, recent work highlights the need to develop treatments for comorbid substance use disorders and GD (Grant and Chamberlain, 2019). The field may benefit from the assessment of brain morphometry in different subgroups based on comorbidities, as well as the type of gambling activity, since strategic gamblers have been shown to display greater gambling severity (Grant et al., 2012). Replication of this work with a greater sample size is also warranted. Interestingly, a recent "mega-analysis" evaluated surface-based morphometry across several substance use disorders. They only reported substance-specific morphometric differences for alcohol use disorder, but not for the other studied substances (i.e., tobacco, cocaine, methamphetamine, cannabis) (Mackey et al., 2019). It might also be interesting to include a substance use disorder comparison group, which would help determine to what extent GD substrates resemble those of substance use disorders. In addition, it might be worth including a GD group without substance use disorders (i.e., tobacco use disorder), as was done in a previous voxel-based morphometry study, which showed differences between patients with as compared to without substance use disorders (i.e., in the precuneus and post-central gyrus) (Zois et al., 2017).

4.2. Conclusion

In conclusion, findings from this work indicate that morphometric substrates in GD mostly resembled those of Internet Gaming Disorder and substance use disorders. Also, the used data-driven surface-based approach particularly highlighted the involvement of the occipital cortex in GD. The occipital cortex might be a relevant substrate for substance use disorders and Internet Gaming Disorder as well, since they share substrates with GD. Further investigation of the possible clinical relevance of the occipital cortex is warranted.

5. References

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Chapter 3: Clinical and cognitive correlates of resting state functional connectivity in adults with gambling disorder

Résumé

Introduction : Le trouble du jeu de hasard et d'argent est un trouble psychiatrique débilitant avec un haut niveau de rechutes. Il y a très peu de connaissances concernant l'activité du cerveau au repos en lien avec les corrélats cliniques et cognitifs. Pourtant, cette ligne de recherche semble importante, car elle pourrait identifier des régions à cibler avec la neuromodulation non invasive pour améliorer les symptômes chez les joueurs pathologiques.

Objectifs : L'objectif principal de ce travail était d'examiner s'il y avait des liens entre la connectivité fonctionnelle au repos et les symptômes cliniques et cognitifs chez les joueurs pathologiques.

Méthode : Nous avons testé des corrélations entre la connectivité fonctionnelle au repos du cerveau en utilisant deux techniques, soient l'analyse par la théorie des graphes et l'analyse par composantes indépendantes. Nous avons mesuré la sévérité du trouble du jeu de hasard et d'argent avec le « South Oaks Gambling Screen », la durée du trouble du jeu de hasard et d'argent, l'impulsivité avec le « Barratt Impulsiveness Scale », la prise de risque avec le « Balloon Analog Risk Task » et les symptômes dépressifs avec le « Beck Depression Inventory ».

Résultats : Les analyses par la théorie des graphes ont démontré deux corrélations avec le niveau de prise de risque, c'est-à-dire, une corrélation positive avec l'efficacité globale, ainsi qu'une corrélation négative avec la longueur moyenne des chemins de l'opercule frontal droit. De plus, les analyses par composantes indépendantes ont démontré que le niveau d'impulsivité et la sévérité du trouble du jeu de hasard et d'argent était corrélé positivement avec la connectivité fonctionnelle

d'un réseau occipital. Enfin, le niveau de symptômes dépressifs était corrélé négativement avec la connectivité fonctionnelle d'un réseau cérébelleux.

Conclusions : Nos résultats suggèrent un besoin de recherche supplémentaire afin de déterminer plus précisément le rôle de l’opercule frontal, du cortex occipital et du cervelet dans les symptômes cognitifs et cliniques. Nos résultats suggèrent également la possibilité de cibler ces structures pour traiter les patients avec trouble du jeu de hasard et d'argent.

Bouchard, A. E., M. Dickler, E. Renauld, C. Lenglos, F. Ferland, C. Rouillard, J. Leblond and S. Fecteau. Clinical and cognitive correlates of resting state functional connectivity in adults with gambling disorder.

Title: Clinical and cognitive correlates of resting state functional connectivity in adults with gambling disorder

Running title: Gambling resting state functional connectivity

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ABSTRACT

Background and aims: Gambling Disorder (GD) is a debilitating psychiatric disorder that has high relapse rates. Little is known on brain activity at rest regarding clinical and cognitive correlates, which could help identify brain regions to target with non-invasive neuromodulation approaches to improve symptoms in GD. Hence, the goal of this work was to study the association between resting state functional connectivity using whole-brain analyses and clinical and cognitive symptoms in patients with GD. Methods: We assessed resting state functional connectivity with data-driven, whole-brain graph theoretical and independent component analyses. We measured GD severity with the South Oaks Gambling Screen, GD duration, impulsivity with the Barratt Impulsiveness Scale, risk-taking with the Balloon Analog Risk Task, and depression with the Beck Depression Inventory. Results: Graph theoretical analyses showed that risk-taking level positively correlated with global efficiency and negatively correlated with average path length of the right frontal operculum. Independent component analysis demonstrated that GD severity and impulsivity level positively correlated with functional connectivity of an occipital network. Also, depressive symptom level negatively correlated with functional connectivity of a cerebellar network. Discussion and Conclusions: This work supports the further investigation of occipital, frontal opercular, and cerebellar regions for cognitive and clinical symptoms that may serve as treatment targets in patients with GD.

Key words: Gambling Disorder, cognitive functions, frontal operculum, occipital cortex, cerebellum, resting state functional connectivity

HIGHLIGHTS

-This study examined whole-brain functional connectivity in gambling disorder.

-Frontal opercular efficiency positively correlated with risk-taking.

-Occipital functional connectivity positively correlated with gambling severity.

-Occipital functional connectivity also positively correlated with impulsivity.

-These results suggest potential neural substrates to target with treatments.

Gambling Disorder (GD) is a substance-related and addictive disorder (SRAD) illustrated by persistent gambling behaviors that interfere with daily functioning (1). Risky decision-making and impulsivity are strong predictors of relapse and adherence to cognitive behavioral therapy (2, 3), which is the most popular treatment (4). Risky decision-making and impulsivity merit further investigation, considering that cognitive behavioral therapy has low long-term success, mainly due to poor adherence to treatment. It is thus important to understand the relationship between these cognitive processes and brain activity to further therapeutic approaches. Brain activity associated with risk-taking and impulsivity in GD has been studied with task-based functional magnetic resonance imaging (fMRI) by contrasting different stimulus conditions, such as high vs. low risk choices (5). However, little is known on cognitive correlates of intrinsic brain activity at rest.

Intrinsic brain activity such as resting state functional connectivity (rs-FC) may serve as a neurobiological model for cognitive functions in SRADs (6). rs-FC with fMRI examines the spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal (7). The main data-driven techniques to characterize rs-FC are graph theoretical and independent component analysis (ICA). Graph theory measures topological properties of complex networks consisting of regions (nodes) and suprathreshold connections (edges). The brain is thought to reflect small-world network properties, where it performs (e.g., cognitive processes) in an efficient manner through connected nodes that work together with the least amount of edges and with the lowest energy expenditure possible (7, 8). Graph theoretical rs-FC has been associated with cognitive processes in SRADs (9). ICA of whole-brain rs-FC separates the BOLD signal into independent spatial components (e.g., networks) that are temporally correlated, which has also been linked to cognitive processes in GD (10, 11). Thus, graph theory and ICA are complementary data-driven methods to investigate whole-brain rs-FC and identify brain regions that may be potential targets of non-invasive neuromodulation to promote decision-making and impulsivity. They may also help identify targets to alleviate other clinical symptoms such as GD severity.

The goal of this work was to investigate relationships between cognitive and clinical symptoms and whole-brain intrinsic activity using graph theoretical analysis and ICA in patients with GD. Little is known regarding rs-FC and whether it is clinically relevant in patients with GD. The default mode network is the network whose rs-FC is most linked to clinical and cognitive measures in GD, which is in line with previous reports highlighting a key role of this network in the pathophysiology of SRADs (e.g., (12)). More specifically, the default mode network is thought to be implicated in self-referential processing and its disruption may relate to gambling-related ruminations and negative emotions. For example, GD severity was negatively correlated with rs-FC of default mode network regions (posterior cingulate cortex and precuneus) (13, 14) and the amount of cognitive distortions was positively correlated with rs-FC of an ICA-derived default mode network (10). In addition, duration of GD was positively correlated with rs-FC between the insula and default mode network areas (medial prefrontal cortex, temporal-parietal junction) (15). This might reflect neural adaptations reflecting an impaired ability to switch between large-scale networks, including the default mode network, since the insula (part of the salience network) is thought to mediate such switching to enhance attention and working memory (16).

Yet, other networks also appear pertinent for cognition in GD. For example, impulsivity level was positively correlated with rs-FC of a fronto-striatal network (11) and the amount of cognitive distortions was positively correlated with rs-FC of ICA-derived fronto-parietal and limbic networks (of note, 5 networks were investigated) (10). The fronto-parietal (or central executive) network is thought to support cognitive control (17). The roles of fronto-striatal and limbic circuits in cognition seem less clear, although they are associated with reinforcement learning (e.g., (18)), as well as memory and emotions (19), respectively. Lastly, GD severity was positively correlated with rs-FC of an ICA-derived cerebellar network (20). In addition, this study appears to be the only data-driven study that investigated rs-FC of whole-brain networks in GD. Although assessing rs-FC of the cerebellum in GD is in its infancy, emerging work has suggested that disrupted cerebellar activity could contribute to impaired cognitive control in SRADs (21). Altogether, it seems that the default mode

network may be particularly pertinent to the pathophysiology of GD. However, more work is needed as there is little evidence to date and other networks might also be implicated. In addition, it is unclear whether graph theoretical metrics of such networks are associated with clinical or cognitive measures (although GD patients displayed differences in graph theoretical metrics implicating the supplementary motor area and paracingulate gyrus as compared to healthy individuals (22)).

Hence, the goal of this work was to further our comprehension of the clinical relevance of rs-FC in GD by investigating whether there were relationships between cognitive and clinical symptoms and whole-brain intrinsic activity using ICA and graph theoretical analysis. Although this literature is still scarce, we hypothesized associations between GD severity and rs-FC of default mode network regions (e.g., posterior cingulate cortex, precuneus) (13, 14), as well as between GD duration and rs-FC of insular-medial prefrontal and insular-temporoparietal circuits (15). In addition, we predicted relationships between risk-taking and impulsivity with the frontal cortex, given the importance of this region in these cognitive processes in patients with GD (e.g., task-based fMRI: (23)). Lastly, we explored for possible rs-FC correlates of depressive symptoms since patients with GD often display depression. The lifetime prevalence of comorbid Major Depressive Disorder is 54% in patients with GD (24). In addition, higher depression levels are associated with greater GD severity (25), as well as worse treatment outcomes (26), and may predict the high suicide rate observed in GD. Indeed, the suicide-related mortality is 15-fold higher in GD than in the general population (27).

We recruited eighteen participants who met DSM-5 criteria for GD. Patients were eligible to undergo MRI scanning. Exclusion criteria included a history of substance use disorders in the past year other than regular tobacco smoking. Seventeen patients completed the study. One dropped out because of discomfort during the MRI scan and another was excluded due to MR anatomical artefacts. Hence, sixteen patients (seven women; mean±standard deviation (SD): 40.0±16.6 years of age, 13.1±1.5 years of education; five left-handed as assessed by the Edinburgh

Handedness Inventory (28); ten took medications, mostly for depression and anxiety) completed the study.

We measured GD severity in the past year with the South Oaks Gambling Screen (SOGS; (29)) (mean=10.1, SD=3.8) and GD duration (mean=7.6 years, SD=8.3 years). We assessed risk-taking with the Balloon Analog Risk Task (BART (30)) with 30 trials. Patients displayed an average number of adjusted pumps on balloons that did not explode of 31.5 (SD=17.1). We measured impulsivity using the Barratt Impulsiveness Scale (BIS, (31)) (mean=68.7, SD=12.8). We assessed depressive symptoms with the Beck Depression Inventory (BDI; (32)) (mean=17.9, SD=9.9). These assessments were conducted before the rs-FC scans, on the same day.

We performed whole-brain MR scan acquisitions with a Philips 3T Achieva scanner (Philips Healthcare, The Netherlands, standard 8-channel head coil). We acquired T1-weighted structural magnetic images with a magnetization prepared rapid acquisition gradient-echo sequence: TR=8.2ms, TE=3.7ms, FoV=250mm, flip angle=8◦, 256×256 matrix, 180 slices/volume, slice thickness=1mm, no gap. For fMRI, we collected EPI BOLD scans with the following parameters: TR=3000ms, TE=30ms, FoV=224×224×140mm, flip angle=70°, 64×64 matrix, dynamic scans 100, voxel size=3.5×3.5×3.5mm, slice thickness=3.5mm, no gap. We instructed patients to keep their eyes open and rest during the entire scanning session. We preprocessed data using SPM 12 through CONN version 19.c (33) with MATLAB R2019a (Mathworks, Inc., USA). We performed the preprocessing pipeline with a functional smoothing of 7mm full width at half Gaussian kernel and tissue probability maps and Artifact Detection Tools to identify outliers. We used intermediate settings (97th percentile in normative sample) and defined functional outliers using a global signal z-value threshold of 5 and a subject-motion threshold of 0.9mm. We denoised rs-FC data with an anatomical component-based noise regression approach, as well as scrubbed and realigned data. We then regressed out the effect of rest using its first order derivatives. We performed band pass filtering (.008-.09 Hz) and linear detrending.

We carried out whole-brain graph theoretical analysis to investigate the main graph measures: global efficiency, local efficiency, average path length, betweenness centrality, cost, clustering coefficient, and degree (34). We used a cost threshold of >.15 to ensure that each participant had the same number of network connections. We conducted one-sample *t*-tests with a threshold of *p*-FDR corrected<.05 and, when appropriate, performed Bonferroni corrections with a threshold based on the number of regions for each of the seven graph measures (α=.05/132=.000379).

We performed group-level ICA using the methodology of Calhoun et al. 2001 (35) with G1 FastICA and GICA 3 back-projection, as implemented in CONN. We selected 40 components and a dimensionality reduction of 64. We investigated within functional connectivity of the main visual, default mode, sensorimotor, salience, dorsal attention, fronto-parietal, language, and cerebellar networks. We used the *Compute spatial match to template* tool as implemented in CONN to identify the networks most similar (with the strongest correlations) to the template networks found in CONN. The CONN developers previously independently performed ICA with 497 participants from the Human Connectome Project (https://www.humanconnectome.org). We performed one-sample *t*-tests using a voxel threshold of *p*-uncorrected<.001 and cluster threshold cluster size *p*-FDR corrected<.05. We used REX to compute average connectivity values within each cluster. When appropriate, we performed Bonferroni corrections with a threshold based on the number of clusters in each network: visual (α=.05/1 cluster=.05); default mode (α=.05/1 cluster=.05); sensorimotor (α=.05/4 clusters=.0125); salience (α=.05/6 clusters=.00833); dorsal attention (α=.05/9 clusters=.00556); fronto-parietal (α=.05/5 clusters=.010); language (α=.05/6 clusters=.00833); cerebellar (α=.05/12 clusters=.00417).

We performed Pearson correlations between cognitive or clinical scores and functional connectivity measures, controlling for age, with SPSS® Statistics, version 27 (SPSS Inc., USA). Graph theory analyses revealed that risk taking level negatively correlated with average path length (*r*=-.874, *p*=.000044; **Figure 1a**;

Table 1) and positively correlated with global efficiency of the right frontal operculum (*r*=.867, *p*=.000061; **Figure 1b**). ICA analyses showed that GD severity level positively correlated with the rs-FC of a visual network (*r*=.576, *p*=.025; **Figure 2a**) and impulsivity level positively correlated with rs-FC of the same visual network (*r*=.695, *p*=.0040; **Figure 2b**). In addition, depressive symptom level negatively correlated with rs-FC of a cerebellar network (*r*=-.703, *p*=.0034; **Figure 3**). Finally, there were no other significant correlations between cognitive or clinical scores and functional connectivity measures of the other regions (graph theory) or networks (ICA) that survived corrections for multiple comparisons.

Table 1. Brain regions associated with cognitive and clinical symptoms in patients with gambling disorder.

Graph theoretical metrics of the right frontal operculum associated with risk taking			
	MNI coordinates (x, y, z)	*T* statistic	*p*-FDR
Average path length	41, 19, 05	29.46	<.00001
Global efficiency	41, 19, 05	34.26	<.00001
Independent component analysis metrics of an occipital network associated with impulsivity level and GD severity			
Network regions	Cluster size (number of voxels)	Peak MNI coordinates (x, y, z)	Size *p*-FDR
Occipital pole Inferior lateral occipital cortex Occipital fusiform gyri Lingual gyri Superior lateral occipital cortex Cerebellum crus I Intracalcarine cortex Cerebellum VI Temporal occipital fusiform cortex	8436	-28, -96, -04	<.00001
Independent component analysis metrics of a cerebellar component from a cerebellar network associated with depressive symptoms			

Network regions	Cluster size (number of voxels)	Peak MNI coordinates (x, y, z)	Size *p*-FDR
Left Cerebellum IX Right Cerebellum IX Vermis IX	68	-04, -52, -44	<.01

MNI: Montreal Neurological Institute. All regions in the visual network are bilateral.

Figure 1. Graph theoretical analysis revealed correlations between risk-taking level and a) average path length as well as b) global efficiency of the right frontal operculum (circled in green, enlarged to improve visibility). The size of the circles represents *t*-statistics of connectivity strength.

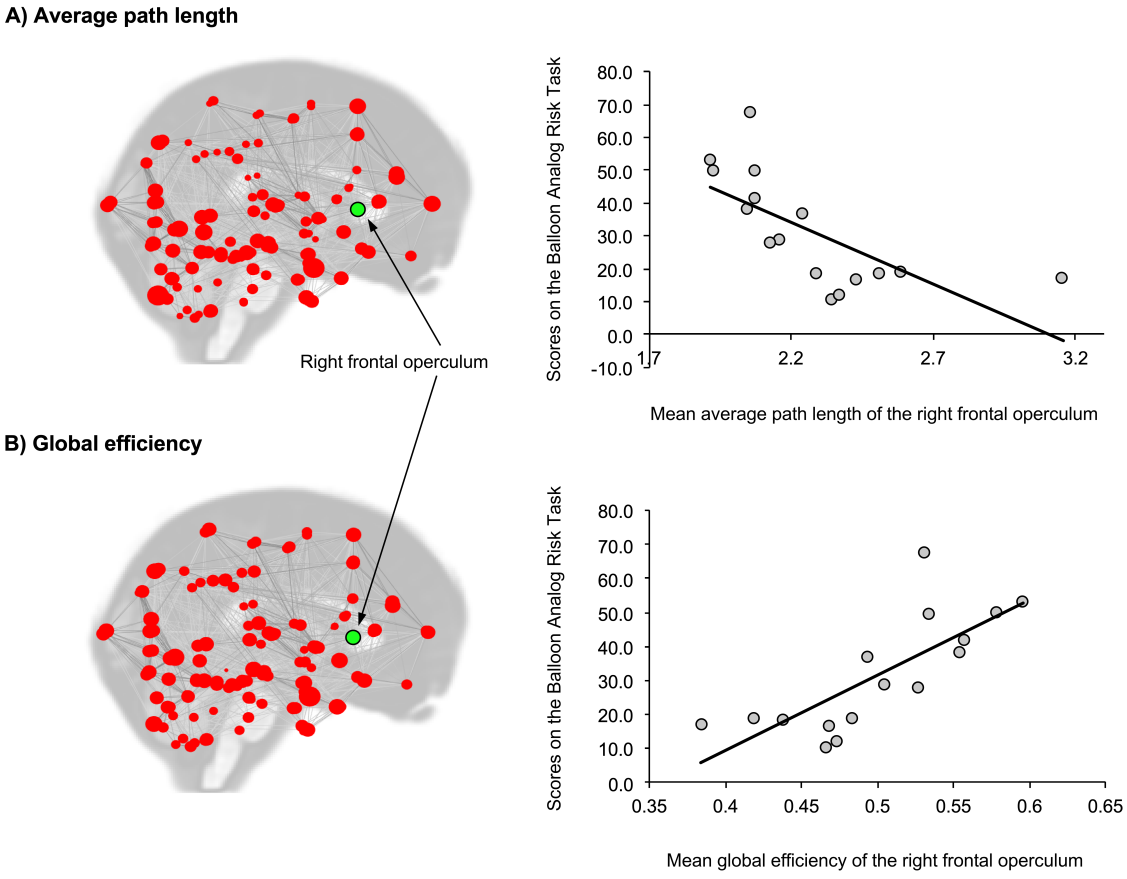


Figure 2. Independent component analysis showed correlations between a) gambling disorder severity and resting state functional connectivity (Fisher transformed correlation coefficients) of a visual network and b) impulsivity level and this same visual network.

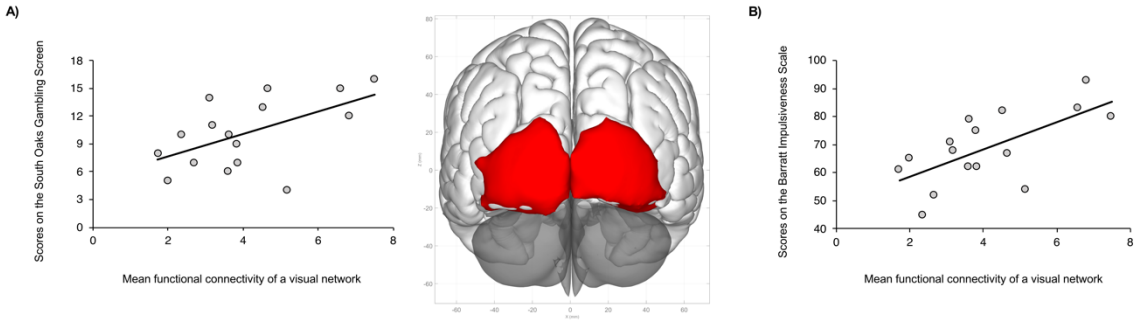
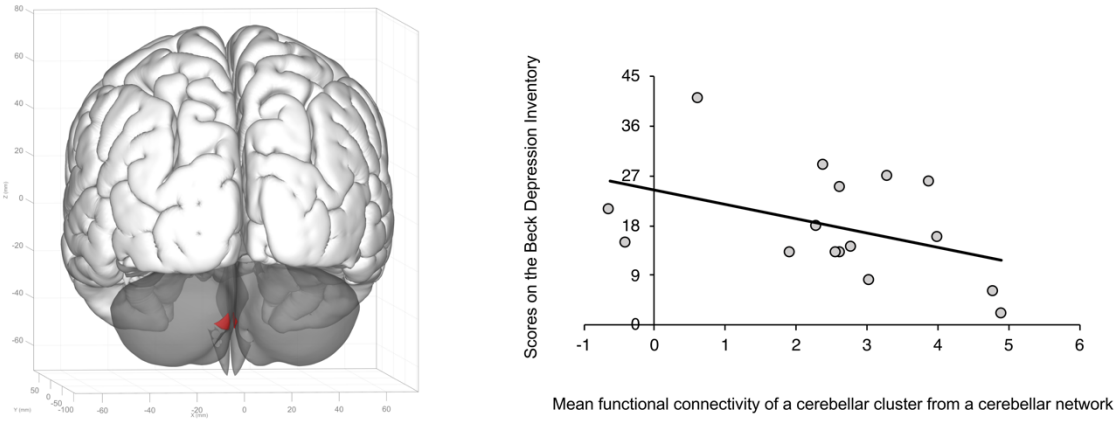


Figure 3. Independent component analysis indicated a correlation between depressive symptoms and resting state functional connectivity of a cerebellar network.



The aim of this study was to explore the cognitive and clinical correlates of functional connectivity in GD. Main findings suggest that the frontal operculum might be an important substrate for risk-taking in patients with GD, where greater efficiency and centrality of this region (shown by graph theoretical global efficiency and average path length) is related to higher risk-taking. Efficiency and centrality are thought to reflect strong and direct communication from a given region with the rest of the brain (8), which is associated with cognitive performance. For instance, greater fronto-limbic efficiency positively correlated with higher impulsivity in Internet Gaming Disorder (9). Patients with greater risk-taking level might display high efficiency and centrality of this network, potentially reflecting powerful information exchange between the frontal operculum and the rest of the brain. This supports previous work showing greater rsFC of circuits implicating the right frontal operculum in GD as compared to healthy individuals (22) and greater activity of the right inferior frontal gyrus during high as compared to low risk decision-making processes (5). Such increased activity in the inferior frontal gyrus might be particularly significant when patients continue excessive gambling despite risky decision-making and losses, as seen in Internet Addiction Disorder, where patients displayed greater activity of the left inferior frontal gyrus during consecutive losses (and consecutive wins but to a lesser extent) as compared to discontinuous losses or wins on a decision-making task (36). This is interesting since these individuals display high impulsivity level as observed in GD (37). However, this should be interpreted with caution as Internet Addiction Disorder is not yet recognized as a SRAD.

Our results also suggest that the cognitive correlates observed in this study are related to rs-FC of a highly efficient but costly random network, and not so much to a cost-efficient, economical small world network (8), since there were no associations between these cognitive performances and other graph theoretical measures (i.e., clustering coefficient, local efficiency, degree, cost, betweenness centrality). Our results support that the right frontal operculum might promote dysfunctional, risky decision-making in patients with GD. To better illustrate, one could think of a social media network, where an influencer must efficiently

communicate information to influence their followers. In this work, our results suggest that the frontal operculum is a foremost neural “influencer” in the neural network of GD.

Results from this work also showed that GD severity and impulsivity level positively correlated with rs-FC of a visual network, including the occipital cortex. The interpretation is unclear, as this seems to be the first whole-brain rs-FC study to find this result. However, our finding complements previous work in GD demonstrating associations implicating impulsivity and GD severity with occipital GABA and Glx (glutamate + glutamine), respectively (38), as well as both greater occipital rsFC (20) and gambling cue-induced activations (39) in GD as compared to healthy individuals. More work is needed to better understand the involvement of the occipital cortex in GD.

In addition, our work showed that depressive symptoms negatively correlated with rs-FC of a cerebellar network. This appears to be the first study to associate depressive symptoms with the cerebellum in GD, complementing previous findings of altered cerebellar rs-FC (20). It might also suggest a potential role of the cerebellum in both mood and reward processing, as higher depressive symptoms predicted greater gambling cue-induced activity of the cerebellum in GD (39). Our results are in line with other studies showing a key role of the cerebellum, such as altered cerebellar rsFC in patients with Methamphetamine Use Disorder and comorbid affective symptoms (40), as well as associations between cerebellar volume and anhedonia severity (often linked to reward-related behaviors (41)) in patients with various psychiatric disorders (including Cocaine Use Disorder, Opioid Use Disorder and Major Depressive Disorder) (42).

To conclude, this preliminary study proposes the frontal operculum, occipital cortex and cerebellum as potential neural substrates of GD, complementing previous work that showed associations between rs-FC and GD severity (20) or cognitive processes (e.g., impulsivity (11)). Further investigation is warranted since these

results come from a preliminary study of a small sample of patients with GD who had comorbidities (tobacco smoking, depression) and took medications. Future work should compare subgroups of patients with and without psychiatric comorbidities. The inclusion of healthy control participants would also further clarify the clinical significance of these findings. Such investigations will likely contribute to identifying neural substrates to target with non-invasive neuromodulation to alleviate gambling symptoms.

Ethical statement

The study was conducted according to the Declaration of Helsinki. The institutional review board of the CIUSSS-CN approved the study (#374). All participants were informed about the study and provided written informed consent.

Author contributions

Amy E. Bouchard: Validation, Formal analysis, Writing - Original draft, Reviewing and Editing, Visualization. Maya Dickler: Investigation, Writing - Reviewing and Editing. Emmanuelle Renauld: Writing - Reviewing and Editing. Christophe Lenglos: Investigation, Writing - Reviewing and Editing. Francine Ferland: Conceptualization, Writing - Reviewing and Editing. Claude Rouillard: Writing - Reviewing and Editing. Jean Leblond: Formal analysis, Writing - Reviewing and Editing. Shirley Fecteau: Conceptualization, Methodology, Validation, Investigation, Resources, Supervision, Project Administration, Writing - Reviewing and Editing, Funding Acquisition.

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Declaration of interest

None.

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Chapter 4: Concurrent transcranial direct current stimulation and resting state functional magnetic resonance imaging in patients with gambling disorder

Résumé

Introduction : La stimulation transcrânienne à courant direct (tDCS) appliqué sur le cortex dorsolatéral prefrontal (DLPFC) pendant que les patients sont au repos peut réduire le « craving » (désir intense pour une substance ou un comportement) chez les patients avec troubles liés à une substance. Par contre, les effets de la tDCS sur l'activité du cerveau au repos n'ont pas encore été étudiés chez les personnes ayant une dépendance autre qu'aux substances.

Objectifs : Cette étude a examiné les effets de la tDCS sur la connectivité fonctionnelle au repos chez les patients avec trouble du jeu de hasard et d'argent.

Méthode : Nous avons effectué une étude combinant la tDCS et l'imagerie par résonance magnétique fonctionnelle. Cette étude a utilisé un devis randomisé, croisé, à double insu et contrôlé par placébo. Les électrodes étaient placées sur le DLPFC (anode sur le DLPFC droit, cathode sur le DLPFC gauche). Les patients ont reçu la stimulation active et placébo pendant 30 minutes lors de deux sessions séparées par sept jours. La connectivité fonctionnelle au repos a été mesurée avant et pendant la stimulation entre le DLPFC et le reste du cerveau.

Résultats : Nos résultats démontrent une augmentation de la connectivité entre le DLPFC droit et le lobule pariétal supérieur droit pendant la stimulation active, comparé à la stimulation placébo. Il y avait également une corrélation positive entre la connectivité de ce réseau et le volume du DLPFC droit.

Conclusions : Une seule session de tDCS ciblant le DLPFC a permis de renforcer

la connectivité fonctionnelle d'un réseau fronto-pariétal. Ce réseau est impliqué dans les fonctions exécutives, notamment dans les patients avec un volume plus élevé de la région sous l'anode.

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Title: Concurrent transcranial direct current stimulation and resting state functional magnetic resonance imaging in patients with Gambling Disorder

Running title: Neuromodulation and neuroimaging in gambling

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Key words: Gambling Disorder, transcranial direct current stimulation, dorsolateral prefrontal cortex, superior parietal lobule, resting state functional connectivity, brain volume

ABSTRACT

Background/Introduction: Transcranial direct current stimulation delivered over the dorsolateral prefrontal cortex while patients are at rest can decrease craving in patients with substance-related and addictive disorders. Yet, the effects of transcranial direct current stimulation on resting state brain activity remain unknown in this population. This study examined the effects of transcranial direct current stimulation on resting state functional connectivity with concurrent stimulation and functional magnetic resonance imaging in patients with Gambling Disorder. Methods: This was a randomized, sham-controlled, double-blind, crossover study. The anodal and cathodal electrodes were applied over the right and left dorsolateral prefrontal cortex, respectively. Patients received 30 minutes of active and sham stimulation on separate days. Resting state functional connectivity was assessed before and during stimulation with seed-based analyses. Results: There was a significant increase of resting state functional connectivity between the right dorsolateral prefrontal cortex seed and the right superior parietal lobule during active stimulation ($p=0.0059$, corrected for multiple comparisons). There was also a positive correlation between resting state functional connectivity change of this fronto-parietal network and brain volume of the right dorsolateral prefrontal cortex ($p=0.0042$, corrected for multiple comparisons). Discussion: A single session of transcranial direct current stimulation targeting the dorsolateral prefrontal cortex strengthened functional connectivity in a fronto-parietal circuit, known to be implicated in cognitive control, especially in patients with greater volume of the region under the anode electrode.

IMPACT STATEMENT

Transcranial direct current stimulation increased functional connectivity of a fronto-parietal circuit in patients with gambling disorder. Changes induced by transcranial direct current stimulation on functional connectivity were larger in patients with greater volume of the dorsolateral prefrontal cortex. Transcranial direct current stimulation strengthened connectivity of a brain network known to be associated with cognitive control.

INTRODUCTION

Gambling Disorder is a psychiatric disorder characterised by problematic gambling behavior leading to important impairment (Potenza et al. 2019). Craving is central to Gambling Disorder pathophysiology (Spagnolo et al. 2018) and strongly predicts relapse (Smith et al. 2015). Existing treatments do not effectively treat craving (Potenza et al. 2019). For example, only 23% of patients remain abstinent after twelve months of cognitive behavioral therapy (Hodgins et al. 2007), which is considered to be among the most effective treatments (Potenza et al. 2019). Other therapeutic strategies are needed to target craving.

Transcranial direct current stimulation (tDCS) applied over the dorsolateral prefrontal cortex can decrease craving levels in patients with substance-related and addictive disorders (Jansen et al. 2013). tDCS holds potential to reduce gambling craving as well (Hone-Blanchet et al. 2015). For instance, tDCS applied over the dorsolateral prefrontal cortex decreased craving in one patient with Gambling Disorder (Martinotti et al. 2018) and in patients with substance-related and addictive disorders and Gambling Disorder (mainly poly users) (Martinotti et al. 2019). Most of these studies applied tDCS while patients were at rest. However, it seems that no studies investigated tDCS-induced effects on resting state functional connectivity (rsFC) during stimulation in Gambling Disorder. Thus, our goal was to identify the impact of tDCS applied over the dorsolateral prefrontal cortex on rsFC during stimulation with concurrent tDCS and rsFC in patients with Gambling Disorder. We previously characterized tDCS-induced changes on rsFC in healthy individuals with concurrent tDCS and fMRI. We found that tDCS over the dorsolateral prefrontal cortex increased rsFC of a fronto-parietal circuit (Mondino et al. 2020). It has also been shown that patients with Gambling Disorder display abnormally weak rsFC between the dorsolateral prefrontal cortex seed and parietal cortex (Bae et al. 2017). Based on these studies, we hypothesized that tDCS will increase rsFC of a fronto-parietal circuit. Additionally, we previously observed positive correlations between tDCS-induced elevations of prefrontal gamma aminobutyric acid levels and volume and

thickness of the dorsolateral prefrontal cortex in patients with Gambling Disorder (Bouchard et al. 2020). Thus, our second goal was to examine whether brain morphometry influences tDCS-induced changes of rsFC strength. We predicted positive correlations between tDCS-increased rsFC of a fronto-parietal network and volume and thickness of the dorsolateral prefrontal cortex, regions under the electrodes.

METHODS AND MATERIALS

Design

This was a randomized, crossover, sham-controlled, double-blind study. Patients underwent two concurrent tDCS/fMRI sessions (active, sham tDCS), separated by seven days. They were randomized with a 1:1 ratio (active or sham). We administered a standardized tDCS side effect form at each session. We assessed blinding integrity in patients and outcome assessor with a standardized form after each session.

Participants

We recruited 18 patients who met DSM-5 criteria for Gambling Disorder and were eligible to receive tDCS (Keel, Smith, and Wassermann 2001) and MRI. They were free of Substance-Related and Addictive Disorders, except for Tobacco Use Disorders, in the past year. Seven patients were taking medications, mainly for depression, and were stable on their medications for at least three months prior to their participation. We recruited patients at the Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale and obtained their written informed consent prior to their participation. The study received ethical approval (#374) from the Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale.

Intervention

tDCS was delivered with an MR-compatible battery-driven stimulator (NeuroConn

GmbH, Germany) that was placed in the operator room and connected to two 7×5cm² rubber electrodes through isolated optical cable with filtering system. The anode and cathode electrodes were placed over the right and left dorsolateral prefrontal cortex, respectively, using the international electroencephalography 10-20 system (F4, F3). Active stimulation was delivered for 30 minutes at a current intensity of 1mA (this device does not stimulate above 1mA) with ramp up and down periods of 30 seconds. Sham stimulation was delivered for 30 minutes with no active current between the 30-second ramp-up and down periods (Gandiga, Hummel, and Cohen 2006). We firstly acquired a 6-minute T1 and a 5-minute fMRI scan. We then started stimulation and acquired an fMRI scan during the last 5 minutes of the 30-minute stimulation period. Patients were instructed to rest and keep their eyes open during scanning.

Measures

Morphometry assessment

We used CBrain (Sherif et al. 2014) to perform FreeSurfer's recon-all pipeline with default parameters (version 6.0.0) (https://surfer.nmr.mgh.harvard.edu). We labelled the dorsolateral prefrontal cortices using the Desikan-Killiany-Tourville protocol (Klein and Tourville 2012), where the dorsolateral prefrontal cortex corresponded to the rostral middle frontal gyrus.

fMRI data acquisition

Whole-brain MRI scan acquisitions were performed with a Philips 3T Achieva scanner (Philips Healthcare, The Netherlands; standard 8-channel head coil). T1-weighted structural magnetic images were acquired with a magnetization prepared rapid acquisition gradient-echo sequence TR=8.2ms, TE=3.7ms, FoV=250mm, flip angle=8◦, 256×256 matrix, 180 slices/volume, slice thickness=1mm, no gap. For the rsFC scans, EPI BOLD images were acquired with the following parameters: TR=3000ms, TE=30ms, FoV=224×224×140mm, flip angle=70°, 64×64 matrix, dynamic scans 100, voxel size=3.5×3.5×3.5mm, slice thickness=3.5mm, no gap.

Analyses

fMRI preprocessing

We preprocessed structural and functional volumes using SPM 12 (www.fil.ion.ucl.ac.uk/spm/) through CONN version 19.c (Whitfield-Gabrieli and Nieto-Castanon 2012). Both CONN and SPM ran on MATLAB R2019a (Mathworks, Inc., USA). We used the Harvard-Oxford Atlas (Desikan et al. 2006) to label the cortical and subcortical areas and the AAL atlas to label the cerebellum (Tzourio-Mazoyer et al. 2002), as implemented in CONN. We performed CONN's default preprocessing pipeline with a functional smoothing of 7mm full width at half Gaussian kernel. We used CONN's default tissue probability maps and Artifact Detection tools to identify outliers. We used intermediate settings (97th percentile in normative sample) and defined functional outliers using a global signal z-value threshold of 5 and a subject-motion mm threshold of 0.9mm. Patients with more than 15% outlier scans were rejected. From the 18 recruited patients, 17 completed the study as one dropped out at the first session because of MRI-related discomfort. Due to technical problems with the stimulation cables in the magnetic field, two patients were excluded. Two other patients were excluded due to MRI artefacts. Thus, from the 18 recruited participants, 13 participants (five women; mean age±SD: 37.4±16.7 years; mean years of education: 13.0±1.4 years; five left-handed as assessed by the Edinburgh Handedness Inventory) (Oldfield 1971) were entered into the analyses (effect size dz=0.85, α=0.05 and power=80%, two-tailed paired samples t-test using G*Power (Faul et al. 2007), taking into five drop outs or rejections).

We used CONN's quality analysis reports to verify preprocessing steps. We performed denoising, using a component-based noise regression method to regress out physiological sources of noise (signals from white matter and cerebrospinal fluid, 20 confound dimensions including their first-order derivatives) (Behzadi et al. 2007). Furthermore, we regressed out movement-related covariates (scrubbing and realignment (with its first order derivatives)) and session effects (before, during active and sham stimulation, each with their first order derivatives). Lastly, we applied band pass filtering of 0.008-0.09 Hz (Hallquist, Hwang, and Luna 2013) and

linear detrending. We used CONN's quality analysis plots to verify denoising steps. Furthermore, we used Afni (https://afni.nimh.nih.gov) to create an analysis mask that excluded voxels whose data were unusable (orbitofrontal cortex).

Seed-based functional connectivity

We performed seed-based functional connectivity analyses with the right and left dorsolateral prefrontal cortex as seeds (±x=36 y=29 z=38, with 5mm radii) using CONN. Seed-based correlation analysis is defined as the Fisher-transformed bivariate correlation coefficients between the seed BOLD time series and an individual voxel BOLD timeseries (Lv et al. 2018) from the entire brain. We used a 2×2 (Stimulation×Time) repeated-measures ANOVA to examine whether there were significant tDCS-induced effects on rsFC. We used a voxel threshold of p-uncorrected <0.001 and cluster threshold cluster size p-FDR (false discovery rate) corrected <0.05 (Friston et al. 1994). If results were significant, we used REX (https://whitfield-gabrieli.sites.northeastern.edu/software/) to compute average connectivity values within our clusters from CONN's graphic user interface. Correlations were bootstrapped 1000 times using a 95% confidence interval to verify robustness and were controlled for age. If appropriate, we used Bonferroni test to correct for multiple comparisons of the correlations with an α threshold p=0.05/4 for the morphometric measures (right dorsolateral prefrontal cortex thickness, volume, left dorsolateral prefrontal cortex thickness, volume=0.0125). Post-hoc and correlation analyses were performed using SPSS, version 26 (IBM Corp, USA).

RESULTS

Effects of tDCS on resting state functional connectivity

We first tested whether there were differences on rsFC between sham and active stimulation conditions at baseline. There were no differences between conditions for both seeds (right dorsolateral prefrontal cortex, p-FDR>0.22; left dorsolateral prefrontal cortex, p-FDR>0.26).

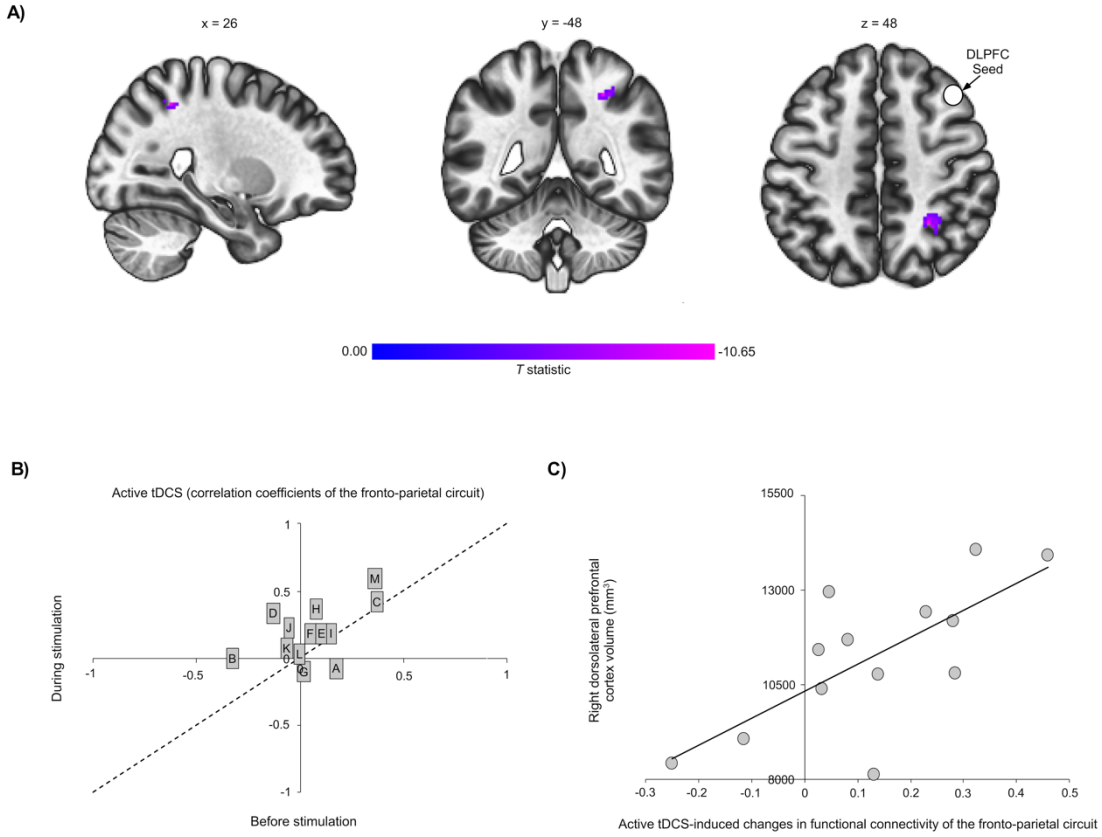
Seed-based functional connectivity analyses revealed a significant Stimulation × Time interaction on rsFC between the right dorsolateral prefrontal cortex seed (under the anode electrode) and a cluster that encompassed the right superior parietal lobule (Figure 1a,b, Table 1). Post-hoc t-tests indicated that active as compared to sham tDCS increased rsFC of this fronto-parietal network during stimulation. In addition, rsFC increased from before to during active stimulation and decreased from baseline to during sham stimulation. Lastly, there was no significant Stimulation × Time interaction on rsFC using the left dorsolateral prefrontal cortex seed (under the cathode electrode).

Table 1. Significant effect of tDCS on resting state functional connectivity and post-hoc comparisons.

	Time x Stimulation repeated measures ANOVA			
	Cluster region	Cluster size (number of voxels)	Peak MNI coordinates (x, y, z)	Size *p*-FDR
R DLPFC seed				
	R SPL	47	26, -48, 48	0.028
	Post-hoc paired *t*-tests			
		t	*p*	Glass's Δ
Before tDCS (active vs. sham)		1.899	0.0818	
During tDCS (active vs. sham)		-3.339	0.00590	
Before vs. during sham tDCS		3.337	0.00592	-0.672
Before vs. during active tDCS		-2.517	0.0271	0.608
L DLPFC seed				
	No significant cluster (*p*-FDR>0.43)			

R: right; L: left; DLPFC: dorsolateral prefrontal cortex; SPL: superior parietal lobule; MNI: Montreal Neurological Institute

Figure 1. **A)** Significant main effect of tDCS on resting state functional connectivity indicating increased connectivity in a fronto-parietal circuit for active as compared to sham tDCS. **B)** Direction of the effects during active tDCS. **C)** Significant correlation between right DLPFC volume and tDCS-induced effects on resting state functional connectivity of the fronto-parietal circuit.



Correlation between tDCS-induced changes on resting state functional connectivity and brain morphometry

There was a positive correlation between active tDCS-induced changes in rsFC of the fronto-parietal network and volume of the right dorsolateral prefrontal cortex (r=0.813, p=0.0042; Figure 1c). There were no correlations that survived Bonferroni corrections between rsFC for active and sham tDCS and the other brain morphometric measures (active: right dorsolateral prefrontal cortex thickness (p=0.15); left dorsolateral prefrontal cortex volume (p=0.20) and thickness (p=0.38);

sham: right dorsolateral prefrontal cortex volume (p=0.043), and thickness (p=0.35); left dorsolateral prefrontal cortex volume (p=0.58) and thickness (p=0.74)).

Side effects and integrity of blinding

There were no significant differences in the number of reported side effects from the participants between active and sham tDCS (p=0.35; Table S1). Eight out of 13 patients guessed correctly whether they received active or sham tDCS with a confidence level of 80% as determined on a visual analog scale. The outcome assessors had minimal interaction with the patients and remained blinded to the stimulation conditions with a confidence level of 100%.

Table S1. Number of patients reporting tDCS-related side effects.

Side effects	Sham	Active
Headache	0	1 (moderate)
Neck pain	1 (mild)	0
Scalp burning	0	1 (mild)
Impaired hearing	0	0
Impaired cognition	1 (mild)	0
Difficulty concentrating	1 (mild)	1 (mild)
Mood changes	0	1 (mild)
Tingling	6 (mild)	6 (mild)
Warm sensation	0	2 (mild)

Side effects are rated as absent, mild, moderate or severe.

DISCUSSION

Our findings indicate that active as compared to sham tDCS increased rsFC of a fronto-parietal network. This circuit encompassed the right dorsolateral prefrontal cortex seed (under the anode electrode) and the right superior parietal lobule. This is in line with previous results in healthy individuals showing rsFC strengthening of this network during and after tDCS (Mondino et al. 2020). Moreover, as seen in this study (Mondino et al. 2020), there was a decrease in rsFC of this fronto-parietal network for the sham tDCS condition. This decrease may reflect a time-related

variation in the intrinsic BOLD signal occurring while subjects are at rest for more than half an hour in the MRI scanner. A resting state fMRI/EEG study found diminished BOLD signal in the fronto-temporal network with increased alpha activity (Goldman et al. 2002) and a resting state PET/EEG study observed decreased blood flow in the left dorsomedial PFC and augmented alpha activity (Sadato et al. 1998). Our findings might thus indicate that dorsolateral prefrontal cortex activity reduces and decorrelates from the other structures such as the parietal regions during the sham tDCS condition, whereas active tDCS interrupts this.

Increasing rsFC of the fronto-parietal network may be clinically relevant in Gambling Disorder. The fronto-parietal circuit has been reported altered in Gambling Disorder (Bae et al. 2017), as well as in internet gaming disorder (Yuan et al. 2016) and substance-related and addictive disorders (Sutherland et al. 2012). Specifically, patients with Gambling Disorder displayed weaker rsFC between a left dorsolateral prefrontal cortex seed and the left postcentral gyrus as compared to healthy individuals (Bae et al. 2017). Further, the fronto-parietal network is implicated in cognitive control (Seeley et al. 2007), which may suppress craving (Verdejo-Garcia, Garcia-Fernandez, and Dom 2019). For instance, 10 tDCS sessions over both dorsolateral prefrontal cortex improved cognitive control which correlated with reduced craving in patients with Methamphetamine Use Disorder (Alizadehgoradel et al. 2020).

Results from this work also suggest that larger right dorsolateral prefrontal cortex volume correlated with greater strengthening of the fronto-parietal rsFC induced by tDCS. A voluminous dorsolateral prefrontal cortex might contain more pyramidal neurons that respond more to tDCS. Indeed, pyramidal neurons respond better to direct current (Radman et al. 2009) and more neurons are seen in a more voluminous structure (de Sousa and Proulx 2014), as shown in animal studies. Brain volume might thus be a useful predictor of tDCS-induced changes in rsFC and neurotransmitter levels (15). This also indicates that tDCS parameters may be

tailored to a patient's brain morphometry, especially for the regions under the electrodes, to achieve the optimal dosage to modulate brain activity.

CONCLUSIONS

Altogether, modulation of fronto-parietal rsFC with tDCS may be clinically relevant for Gambling Disorder, especially for patients with greater dorsolateral prefrontal cortex volume. Although our sample was relatively small, we used strict processing measures to control for type 1 error to provide adequate power analysis for needed replication studies. It remains to be seen whether repeated tDCS sessions can induce lasting increase of rsFC of this circuit to improve cognitive control and help patients resist gambling.

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Authorship confirmation statement

SF and FF designed the study. MD and FF recruited patients. MD, CL and SF collected data. AEB led the data analysis with the participation of MD and ER. AEB led the interpretation of results with the participation of MD. AEB and MD drafted the paper. All authors critically reviewed the paper and approved the finalized paper.

Authors disclosure statements

None

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Data statement

Data are available upon request to the corresponding author.

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Chapter 5: The impact of brain morphometry on tDCS effects on GABA levels

Résumé

Introduction : La stimulation transcrânienne à courant direct (tDCS) appliquée sur le cortex dorsolatéral prefrontal (DLPFC) peut augmenter le niveau de GABA dans le cerveau pendant la stimulation. Par contre, le rôle potentiel de la morphométrie du cerveau sur ces changements pendant la stimulation demeure inconnu.

Objectifs : Notre objectif était d'examiner si la morphométrie du DLPFC influence les effets de la tDCS sur les neurotransmetteurs pendant la stimulation.

Méthode : Nous avons utilisé l'imagerie par résonance magnétique structurelle pour mesurer la morphométrie du DLPFC. Nous avons utilisé les données d'une étude antérieure réalisée par notre équipe (Dickler et al. 2018) pour mesurer le niveau de neurotransmetteurs modulé par la tDCS.

Résultats : Nous démontrons une corrélation positive entre le volume du DLPFC et l'augmentation de GABA frontal induit par la tDCS pendant la stimulation.

Conclusions : Cette étude suggère que la morphométrie du site de stimulation peut influencer les effets de la tDCS sur les substrats neuronaux. Cette mesure pourrait donc être considérée pour prédire la réponse à la neuromodulation non invasive.

Abstract

Introduction: Transcranial direct current stimulation (tDCS) delivered over the dorsolateral prefrontal cortex (DLPFC) can increase GABA level in the brain during stimulation. However, the potential impact of brain morphometry on these changes during stimulation are unknown.

Objectives: Our objective was to examine whether morphometry of the DLPFC influences tDCS-induced effects on neurotransmitters during stimulation.

Methods: We used structural magnetic resonance imaging to measure DLPFC morphometry. We used data from a previous study conducted by our team (Dickler et al. 2018) to measure the level of neurotransmitters modulated by tDCS.

Results: There was a positive correlation between volume of the DLPFC and tDCS-induced elevations of frontal GABA level during stimulation.

Conclusions: This study suggests that morphometry of the stimulation site can influence tDCS effects on neural substrates. Morphometry might thus be considered to predict response to non-invasive neuromodulation.

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The impact of brain morphometry on tDCS effects on GABA levels

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Highlights

- tDCS can change GABA levels during stimulation.
- Brain morphometry of the area under the cathode electrode can impact tDCS changes on GABA levels.
- Brain morphometry of the areas under the electrodes may be considered to optimize tDCS effects on neurotransmitter levels.

Introduction

Transcranial direct current stimulation (tDCS) applied over both dorsolateral prefrontal cortices (DLPFCs) can change neurotransmitter levels when measured with concurrent magnetic resonance spectroscopy (MRS) [1,2]. For instance, tDCS elevated prefrontal GABA levels in adults with gambling disorder (GD) [1]. Such effect may be clinically meaningful as medications targeting the GABAergic system can reduce craving [3] and impulsivity in GD [4]. However, there are still several unknowns on how tDCS influences brain activity. One factor that may influence tDCS effects is brain morphometry. This is of particular interest for populations known to display altered morphometry, such as GD [5]. Further, animal studies showed that neuron morphology influences electric field stimulation in brain slices. Direct current is thought to favor depolarization of pyramidal neurons in layer V [6]. Considering that a greater number of neurons are found in areas of larger volume [7], one could predict that brain areas with greater cortical volume have more pyramidal neurons that respond to tDCS. The goal of this exploratory study was to investigate the impact of brain morphometry on tDCS effects on GABA levels in adults with GD. We hypothesized that greater tDCS-induced elevation of GABA levels will correlate with greater volume and thickness of the DLPFCs.

Methods

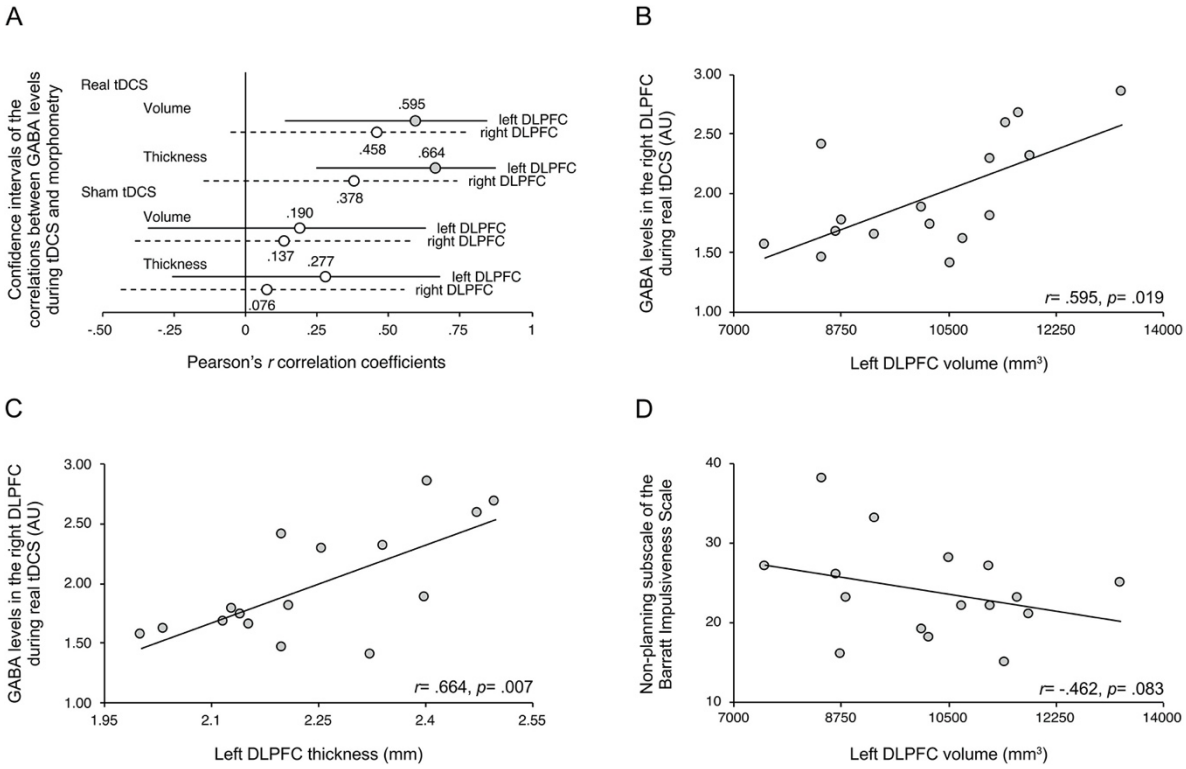
We investigated the impact of brain morphometry on tDCS effects using data from a previous study [1]. This study was randomized, crossover, sham-controlled, and blinded at two levels (blinding assessed in patients and MRS experimenter). Each session, separated by 7 days, comprised an anatomical scan and a session of simultaneous tDCS delivery and MRS acquisition. Eighteen adults were recruited and two were not included in the analyses (one dropped out, one was rejected due to movement artifacts). Sixteen adults (seven women; mean age= 37.8 years, SD= 16.8) who met DSM 5 criteria for GD participated in this study. They provided their informed consent prior to their participation. tDCS was delivered with an MR-compatible DC-STIMULATOR (neuroConn GmbH, Germany). The 35-cm^2 anode and cathode electrodes were placed over the right and left DLPFC, respectively,

based on the 10-20 EEG system (F4, F3). Real tDCS was delivered for 30 min at 1 mA. Sham tDCS was delivered for 30 min with current applied during the first and last 30 sec of the session. Subjects were scanned with a Philips 3 Tesla Achieva scanner (Philips Healthcare, Netherlands). T1-weighted structural magnetic images were obtained with a magnetization prepared rapid acquisition gradient-echo sequence (repetition time= 8.2 ms; echo time= 3.7 ms; field of view= 250 mm; flip angle= 8º; 256 x 256 matrix; 180 slices/volume; slice thickness= 1 mm; no gap). We used CBrain to perform FreeSurfer 6.0.0 recon-all pipeline with default parameters [8] and the Desikan-Killiany-Tourville protocol to label the cortices. Neurotransmitter levels were measured with the MEGA-PRESS acquisition sequence and a 3x3x3 cm^3 voxel of interest in the right DLPFC. GABA levels were analyzed with GANNET 2.0 [9]. Pearson correlations were performed to test for correlations between neurotransmitter levels and morphometry measures, controlling for age. We used SPSS Statistics 26.0 (N.Y., U.S.). Effects were considered significant at p value$\leq$ .05. We applied Bonferroni correction for multiple comparisons within each tDCS site.

Results

For real tDCS, there were positive correlations between tDCS changes in GABA levels in the right DLPFC and morphometric measures of the left DLPFC (volume: r= .595, p= .019; thickness: r= .664, p= .007, after Bonferroni correction; Figure 1a,b,c), but not of the right DLPFC (volume: r= .458, p= .086; thickness= r= .378, p= .165). There were no significant correlations for sham tDCS and morphometric measures of the left DLPFC (volume: r= .190, p= .498; thickness: r= .277, p= .317) or the right DLPFC (volume: r= .137; p= .626; thickness r= .076; p= .788). We then tested whether the left and right DLPFC differed in morphometric measures and found no differences for volume (t(30)= 1.792, p= .083; left DLPFC: mean= 10229.69, SD= 1543.66; right DLPFC: mean= 11311.88, SD= 1857.79) or thickness (t(30)= 1.736, p= .093; left DLPFC: mean= 2.24, SD= .154; right DLPFC: mean= 2.35, SD= .203).

Figure 1. **A)** confidence intervals of correlations between changes in GABA levels in the right DLPFC during tDCS with morphometry of the right and left DLPFC. **B)** correlations between changes in GABA levels in the right DLPFC during tDCS with volume and C) thickness of the left DLPFC, and D) correlation between volume of the left DLPFC and scores at the non-planning subscale of the Barratt Impulsiveness Scale.



We also explored for correlations between morphometric measures of the left and right DLPFC and behaviours related to gambling (i.e., South Oaks Gambling Screen, Barratt Impulsiveness Scale (BIS), and duration of GD) and found no correlations. There was one correlation, although not significant, that indicated a fair relationship between the volume of the left DLPFC and scores at the non-planning subscale of the BIS (r= -.462, p= .083; Figure 1d).

Discussion

Results from this work revealed that brain morphometry influenced tDCS changes in

prefrontal GABA levels. Elevation of GABA levels in the right DLPFC induced by tDCS delivered over both DLPFC was higher for greater volume and thickness of the left DLPFC, the area under the cathode. This may reflect that greater cortical areas comprise more pyramidal neurons that respond to tDCS. This is in line with studies showing that areas containing large pyramidal neurons are more prone to respond to direct current [6]. Results of this study also indicate that smaller volume of the left DLPFC was related with greater impulsivity at the non-planning subscale of the BIS, which evaluates “careful thinking and planning and enjoyment of challenging mental tasks” [10]. In bilateral tDCS montages, it is expected that the current flows from the area under the anode to that under the cathode, here across cortices, from the right to the left DLPFC. Thus, it would be interesting to test for potential changes in GABA levels in the area under the cathode, which we did not due to time constraint (MRS acquisition sequence of 12 min/voxel of interest during the 30-min tDCS delivery). Overall, it seems that patients with smaller volume of the left DLPFC are more impulsive and respond less to tDCS in regards to GABA levels. This may be peculiarly relevant for tDCS studies aiming at modulating GABA levels that consequently may reduce impulsivity in clinical populations that are known to display brain morphometry abnormalities, especially in tDCS targeted areas.

Conflict of interest

The authors declare no conflict of interest.

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Discussion

New treatment options are needed for GD since those that are currently offered show little success. A better understanding of the neural substrates involved may help the development of new treatment approaches. Non-invasive neuromodulation techniques such as tDCS are promising since they can target precise brain regions and circuits relevant to GD. Across four studies, this thesis explored the clinical relevance brain morphometry (study I) and rs-FC (study II) as well as the effects of tDCS on rs-FC (study III) in patients with GD. It also explored whether brain morphometry influenced tDCS-induced effects on rs-FC (study III) and neurochemistry (study IV) in patients with GD. More specifically, this thesis demonstrated the potential clinical relevance of the occipital cortex (studies I and II), as well as the frontal operculum and the cerebellum (study II). Further, it showed that brain morphometry of the DLPFC can influence tDCS-induced effects on increased fronto-parietal rs-FC (study III) and elevated frontal GABA level (study IV). The following is an overarching discussion of these 4 studies, followed by a discussion of limitations and future directions. The next sections discuss potential substrates of GD that may inform treatment approaches.

6.1 Frontal operculum, occipital cortex and cerebellum: potential treatment targets in gambling disorder?

6.1.1 Summary of findings

This thesis proposed that the frontal and occipital cortices, as well as the cerebellum, might serve as GD-related substrates and treatment targets. More specifically, the frontal cortex was thinner in patients with GD as compared to a normative database of healthy individuals. Additionally, rs-FC of the frontal operculum was positively correlated with risky decision-making. Concerning the occipital cortex, it was more voluminous and thicker in patients with GD as compared to norms of healthy individuals. In addition, occipital surface area was positively correlated with depressive symptoms. Also, rs-FC of an occipital network was positively correlated with impulsivity level and GD severity level. Lastly, rs-FC of a cerebellar network was

negatively correlated with depressive symptoms. A better understanding of such substrates might help inform treatment approaches in GD.

6.1.2 Frontal operculum (inferior frontal gyrus) in gambling disorder

6.1.2.1 Frontal operculum substrates and link with cognitive processes related to gambling behaviours

The inferior frontal gyrus (IFG), which contains the frontal operculum, might be an important substrate for GD, since it is implicated in gambling-related behaviours, including craving, cognitive flexibility, and inhibitory control. Firstly, craving is central to the pathophysiology of GD and should be a therapeutic target, as it is a significant predictor of relapse (Smith et al. 2015). Cues (e.g., the sight of individuals gambling, gambling activities) are important triggers for craving. Patients with GD displayed greater activity of the right IFG in response to gambling-related stimuli on cue-provoking paradigms as compared to healthy individuals, which positively correlated with craving level (Crockford et al. 2005). Additionally, another work found that patients with GD showed increased activity of this region when viewing gambling-cues as compared to neutral cues and when compared to activations in healthy individuals (Limbrick-Oldfield et al. 2017). Patients also reported greater cue-induced craving. Despite this, scores were not correlated with this increased activity. Hence work will be needed to investigate the potential role of the frontal operculum in gambling-related craving.

Secondly, there is a line of evidence that the right IFG is implicated in cognitive flexibility. This cognitive function represents the ability to adjust to new rules or demands (Diamond 2013). Patients with GD display weaker cognitive flexibility as compared to healthy individuals (Odlaug et al. 2011). It seems pertinent to consider this cognitive domain, given that it is associated with poorer addiction-related treatment outcomes (Turner et al. 2009). There is a small line of evidence that the right IFG plays a role in this cognitive construct, as assessed by the Probabilistic Reversal Learning Task. To illustrate, patients with GD displayed decreased fMRI activity of the right IFG on two components of this task, that is, during behavioural shifting (i.e., final reversal errors as compared to perseverative errors) (Verdejo-

Garcia et al. 2015) and when responding to financial gains and losses (de Ruiter et al. 2009), as compared to healthy individuals.

Furthermore, the right IFG is purported to play a key role in inhibitory control by serving as a "brake" to pause or stop inappropriate responses (Bari and Robbins 2013; Aron et al. 2014), presumably through a cortico-subthalamic-pallidal-thalamocortical loop (Jahanshahi et al. 2015). Inhibitory control, a component considered part of impulsivity, is central to GD pathophysiology (Ioannidis et al. 2019). Impulsivity is a multifaceted, complex construct with several domains. These include cognitive impulsivity (inability to suppress attentional biases) and motor impulsivity (response inhibition), which reflects the inability to cancel or stop inappropriate responses (e.g., gambling activities or behaviours). Patients with GD displayed impaired performances on response inhibition tasks, as compared to healthy individuals, including the Stop Signal and Go/No-Go tasks (Chowdhury et al. 2017; Penolazzi et al. 2020). Altogether, it seems that the right IFG may be implicated in gambling-related behaviours. One might wonder whether the frontal operculum (inferior frontal gyrus) might be an interesting treatment target for patients with GD, considering its potential clinical relevance in GD.

6.1.2.2 Inferior frontal gyrus: treatment target?

Target engagement is increasingly recognized as an important focus in clinical trials (Insel and Gogtay 2014). Researchers are encouraged to verify whether a treatment engages targets (behaviours, cognitive processes, biological or brain substrates, etc.) and whether potential changes are associated with clinical efficacy (e.g., alleviation of symptoms). The next steps include finding an appropriate dosage and treatment duration to relieve symptoms. Ultimately, the main aim is to advance research and optimise treatment approaches. Psychotherapy, medications, as well as non-invasive neuromodulation could potentially engage substrates and relieve symptoms in patients with GD. These next sections discuss target engagement of the IFG in SRADs.

6.1.2.2.1 Psychotherapy

Psychotherapy can modulate BOLD activity of the IFG in patients with SUDs. Firstly, patients with Opioid Use Disorder that received 4 weeks of combined mindfulness-based therapy and treatment as usual (medications such as mood stabilizers and therapies including CBT) displayed weaker rs-FC of the right IFG as compared to those that received only the treatment as usual (Fahmy et al. 2019). Additionally, in another study, patients with SUDs (cocaine, alcohol, cannabis, or heroin use disorders) underwent an 8-week psychotherapy regimen. More specifically, half received weekly individual and group counseling, whereas the other half received this intervention in addition to twice weekly computerized CBT (DeVito et al. 2012). As compared to before the treatment program, patients displayed less fMRI activity of the right IFG, which was accompanied by improved performance on the Stroop Color-Word Interference Task (smaller reaction time during incongruent trials), which likely reflected improved cognitive control. These results appeared clinically significant, as the rs-FC reductions were correlated with improved mindfulness scores, which might reflect better cognitive control.

Additionally, the IFG may play a role in SUD-related abstinence. For instance, abstinent cocaine users that underwent psychotherapy displayed higher fMRI activity of the left IFG when anticipating wins and losses on the Monetary Incentive Delay Task, as compared to performances by healthy individuals (test-retest differences) (Balodis et al. 2016). In addition, patients with heroin use disorder undergoing abstinence-based therapy displayed increased cue-induced BOLD activity of the right IFG as compared to healthy individuals, but there was no change in craving level (Tabatabaei-Jafari et al. 2014). Interestingly, in the same study, patients who underwent abstinence-based therapy showed greater activity of the right IFG as compared to those that received methadone replacement therapy, which might reflect greater effort to suppress craving in the behavioural therapy group (and a lesser effort in those receiving a neurochemical treatment). There is some evidence that increased IFG activity (and possibly better cognitive control) might predict stronger treatment outcomes. For instance, lower cotinine-nicotine metabolite level (lesser tobacco use) after psychotherapy was negatively correlated

with greater activity of the right IFG during a Stroop task (when comparing incongruent versus congruent trials) in adolescent smokers (Krishnan-Sarin et al. 2013).

6.1.2.2.2 Pharmacotherapy

Pharmacological treatments can influence IFG activity in patients with Alcohol Use Disorder and Methamphetamine Use Disorder. Firstly, detoxified patients with Alcohol Use Disorder received one of two interventions, that is, extended release naltrexone and supportive therapy or a placebo and supportive therapy, for a 2-week period (Lukas et al. 2013). Patients underwent both a visual and an olfactory cue-reactivity task before and after the intervention. Patients who received naltrexone showed decreased visual cue-induced BOLD activity of the left IFG as compared to the placebo group when comparing baseline and post-treatment scans. In another study, patients with Cocaine Use Disorder had decreased BOLD activity of the right IFG while viewing cocaine-related cues as compared to baseline after they received either D-cycloserine or placebo, in addition to 2 cocaine-cue extinction sessions including CBT skills training (Prisciandaro et al. 2013). Furthermore, patients that underwent methadone replacement therapy demonstrated higher BOLD activity of the right IFG on a cue-reactivity paradigm as compared to healthy individuals, which might reflect better inhibitory control (Tabatabaei-Jafari et al. 2014).

6.1.2.2.3 Non-invasive neuromodulation approaches

There is recent meta-analytic evidence that a single tDCS session targeting the IFG can improve inhibitory control in both healthy individuals and clinical populations (including depression and ADHD), on several tasks, e.g., the Stop Signal Task and the Go/No-Go Task (Schroeder et al. 2020). Results from this meta-analysis support targeting the right IFG and not the DLPFC (targeting the former resulted in a medium effect size and the targeting the latter showed a null effect size).

As of now, two tDCS studies targeted the right IFG in SRADs, that is, in patients with Alcohol Use Disorder (Witkiewitz et al. 2019) and in heavy drinkers (but not diagnosed with Alcohol Use Disorder) (Claus et al. 2019) to modulate SRAD-related behaviours including inhibitory control. In one study, patients received either active

of sham tDCS (anodal over the right IFG, cathodal over the left shoulder), coupled with mindfulness-relapse prevention therapy (where patients learn mindfulness techniques to reduce their cue-induced attentional biases to help them resist craving) (Witkiewitz et al. 2019). They displayed reduced drinking over time. Also, those who attended more sessions showed decreased cue-induced craving level and percent heavy drinking days. However, there were no differences between active and sham tDCS on outcome measures (e.g., drinking consumption and inhibitory control (i.e., stop signal reaction time) as assessed using the Stop Signal Task).

In the other study (Claus et al. 2019), heavy alcohol drinkers received 4 sessions of either: 1) active tDCS with real cognitive bias modification; 2) sham tDCS with real cognitive bias modification; 3) active tDCS with sham cognitive bias modification; 4) sham tDCS with sham cognitive bias modification (anodal over the right IFG, cathodal over the left upper arm). Cognitive bias modification was administered using an Approach-Avoidance Task, where participants carried out approach (pulling a joystick) or avoidance (pushing) responses to alcohol-related or control pictures, based on the orientation of the image. In the real cognitive bias modification training, participants were asked to avoid alcohol stimuli and approach control stimuli 90% of the time. In the sham cognitive bias training, participants were asked to equally avoid and approach both types of stimuli. This study demonstrated no significant effects on alcohol approach biases nor alcohol consumption 1-week and 1-month post treatment.

There are several potential explanations for the lack of significant results. Firstly, it is possible that there were too few sessions to induce clinically significant results. Also, participants might not have been motivated enough to change their habits. For example, there is some evidence that patient motivation to quit or reduce the addictive behaviour leads to stronger clinical benefits. For instance, smokers with higher motivation to quit responded had greater reductions in tobacco smoking following tDCS (Vitor de Souza Brangioni et al. 2018)). Furthermore, stimulation parameters might not have been adequate such as electrode size and positioning.

It also remains to be seen whether targeting the IFG leads to significant changes in IFG function (e.g., rs-FC or BOLD activity) that is associated with clinically relevant changes in symptoms. rTMS might also be worth considering. rTMS studies typically use neuronavigation to identify brain targets. For example, a recent study identified individualized right IFG treatment targets (e.g., finding peak task-based MNI coordinates) while tobacco users performed a modified version of the Go/No-Go Task (in addition to the Go and no-go stimuli, the authors employed a rare go trial, in order to investigate whether TBS-induced effects were specific to inhibitory control or novel detection, given that the right IFG is thought to be implicated in both processes) (Newman-Norlund et al. 2020). After, patients received either iTBS or cTBS on 2 separate visits. Patients performed the task before and after the sessions. This study found that iTBS and cTBS induced opposite effects-improving and impairing inhibitory control, respectively, suggesting that the former, but not the latter, strengthened corticothalamic task-based functional connectivity.

Altogether, it seems that treatments can modulate right IFG BOLD activity in patients with SRADs. However, a small number of non-invasive neuromodulation studies targeted the IFG. More research is needed to investigate whether this approach could be promising in patients with GD.

6.1.3 Occipital cortex in gambling disorder

6.1.3.1 Occipital substrates and link with cognitive processes related to gambling behaviours and depressive symptoms

The occipital cortex appears to be mainly implicated in cue-induced craving. Firstly, patients with GD displayed higher occipital BOLD activity in response to gambling-related cues. More specifically, two studies found that patients displayed greater BOLD activity of the left occipital cortex in response to gambling-related cues as compared to healthy individuals (Crockford et al. 2005; Goudriaan et al. 2010), which was positively correlated with craving (Crockford et al. 2005). In another study, patients with GD demonstrated increased BOLD activity of the right middle occipital gyrus during the presentation of gambling-related epochs of videotape viewing as

compared to control epochs (Potenza et al. 2003). In the same work, patients displayed higher cue-induced craving level as compared to healthy individuals.

Additionally, patients showed greater activity of the right occipital cortex in response to gambling-related cues as compared to neutral stimuli accompanied by increased craving (Limbrick-Oldfield et al. 2017). Interestingly, in the same work, patients with GD had increased occipital pole activity when comparing food to neutral stimuli, supporting incentive sensitization to both natural and gambling rewards. These results are in line with the SUD literature. For instance, a meta-analysis reported that 86% (24/28) of studies using a whole-brain approach found significant elevated activity of the occipital cortex (primary and secondary visual cortices) in response to drug-related cues as compared to neutral cues across different SUDs (alcohol, cannabis, cocaine, tobacco use disorders; no activation differences between substances) (Hanlon et al. 2014). Altogether, it seems that the occipital cortex may play an important role in cue-reactivity in SRADs.

Furthermore, the occipital cortex might be implicated in other symptoms relevant for GD, such as cognitive symptoms and depressive mood, particularly in patients with GD that use electronic gaming machines. Electronic gaming machines, including modern slot machines, are fast paced, designed for continuous play, and often contain video screens that display attractive visual signals (flashing lights, bright colours, etc.). It has been recently proposed that highly experienced gamblers (not patients with GD) who use these platforms might be vulnerable to a cognitive state called the “slot machine zone” (Murch and Clark 2021). This occurs when players are immersed in play (similarly to being in a trance) with little regard for non-gambling stimuli (e.g., losing track of time, being completely immersed in the game). Two types of immersion have been proposed, based on prior literature showing associations with positive and negative affect: 1) “zoning in”, where gamblers are captivated by the game; 2) “zoning out”, in which gamblers play to escape or to improve their mood.

Another recent eye tracking study conducted in frequent gamblers (not patients with GD) supported the zoning out hypothesis, as they appeared immersed in actively scanning the game and focusing on the platform's credit window (Murch et al. 2020). One might therefore speculate that the occipital cortex plays a role in this zoning out process. Yet, future work will be needed to determine how exactly patients with GD immerse in the game, especially for those with comorbidities such as depressive symptoms (e.g., considering the need to escape, do they zone in or zone out?). This line of research might also support investigating the potential role of the occipital cortex in these gambling-related behaviours.

Altogether, there is some evidence that the occipital cortex might play an important role in GD substrates. It might therefore be worth targeting this region to modulate its activity. The following sections will explore the current evidence in the fMRI field.

6.1.3.2 Occipital cortex: treatment target?

As of late, behavioural interventions, pharmacological treatments, and non-invasive neuromodulation do not seem to modulate occipital function in patients with GD. Yet, there is a line of evidence that these treatments can modulate activity, as measured by fMRI, in patients with other SRADs that share substrates with GD. One might therefore suppose that these treatments could potentially modulate such activity in patients with GD. The following sections discuss current evidence in the SRAD field, starting with behavioural treatments.

6.1.3.2.1 Psychotherapy

Firstly, tobacco smokers with a history of smoking cessation-related weight gain and relapse displayed reduced right occipital fusiform activity in response to food cues (in comparison to neutral cues) after 1 week of mindfulness therapy and 12-hour smoking and eating abstinence, possibly reflecting decreased cue-related salience (Kragel et al. 2019). Secondly, in another study, adolescents with excessive online game playing showed increased BOLD activity of the left occipital fusiform gyrus during working memory tasks (mental arithmetic calculations such as adding up numbers) after 4 weeks of a behavioural intervention (education to reduce online gaming) (Kim et al. 2012). However, this result should be interpreted with caution,

as it was not FDR-corrected, and the clinical relevance of this result was unclear (e.g., there was no improvement in working memory task performance). More studies are needed to determine whether behavioural treatments can influence occipital activity.

6.1.3.2.2 Pharmacotherapy

Similar to behavioural therapies, pharmacological treatments do not appear to modulate occipital activity in GD. Yet, there is a line of evidence that these treatments can influence occipital function in other SRADs, notably, in patients with Opioid Use Disorder and Alcohol Use Disorder. Firstly, ultra-rapid opioid detoxification under anesthesia combined with 2 weeks of naltrexone decreased rs-FC of the left middle occipital cortex after the intervention in patients with Opioid (Codeine) Use Disorder, which was positively correlated with reduced withdrawal symptoms (Qiu et al. 2016). Another study found that abstinent heroin users who received methadone replacement therapy displayed increased fMRI activity of the lingual gyrus on a cue reactivity task, as compared to healthy individuals, although the clinical relevance is unclear (Tabatabaei-Jafari et al. 2014). Given that patients did not report cue-induced craving, one might wonder whether the observed increased activity might reflect resisting craving. It might also possible that the intensity of craving decreased such that craving is easier to control.

Moreover, abstinent heroin users showed decreased resting state BOLD activity of the occipital cortex following a 1-hour administration of a neuroadaptagen therapy called KB220Z™, as compared to a placebo. This was presumably by activating dopaminergic pathways since KB220Z™ contains amino acid neurotransmitter precursors and enkephalinase-catechol-O-methyl-transferase inhibitors (Blum et al. 2015). The idea behind this treatment is to increase the number of dopamine receptors, since dopamine agonists (e.g., apomorphine) reduce dopamine receptors in the long run, which may encourage the patient to relapse. Furthermore, in another study, patients receiving in-house treatment for Alcohol Use Disorder displayed decreased cue-induced occipital fMRI activity after they received 4 sessions of a chemical aversive (emetic) therapy (i.e., Ipecac, which is plant-based drug that

causes vomiting) (Elkins et al. 2017). This result may be clinically relevant, as patients displayed strong aversion to alcohol, which lasted both 30- and 90-days post-treatment.

6.1.3.2.3 Non-invasive neuromodulation approaches

Not much is known regarding modulating occipital activity in SRADs. One tDCS study found that a single session of tDCS (anode over the right and cathode over the left DLPFC) increased rs-FC of the right lingual gyrus after active tDCS as compared to after sham tDCS in patients with Methamphetamine Use Disorder (Shahbabaie et al. 2018). tDCS applied over the occipital cortex of healthy individuals can also improve cognition. As such, a single session of tDCS over the occipital cortex (anodal over the medial occipital cortex, cathodal over the vertex), as compared to sham, improved performance on a visual working memory task. In this standard change detection task, participants were asked to determine whether a test item (the location or colour of a single dot) was different or similar to a previously presented (<1 sec) memory item (a set of coloured dots)) (Makovski and Lavidor 2014). This finding suggests a possible role of the occipital cortex in visual working memory consolidation (e.g., the ability to maintain visual information that has disappeared to use it in ongoing tasks).

Furthermore, there do not seem to be any studies that targeted the occipital cortex using rTMS in the SRAD field. Studies have primarily focused on targeting the left or right DLPFC (Ekhtiari et al. 2019; Jansen et al. 2013). Interestingly, there is some evidence that targeting the occipital cortex can modulate visual memories in healthy individuals, possibly as a bottom-up approach, where the occipital cortex works with higher order brain regions including the PFC (van de Ven and Sack 2013). Considering that addiction may be a “disease of learning and memory” (Hyman 2005), one might wonder whether targeting the occipital cortex could help inhibit cue-induced addiction-related visual memories to help patients resist craving (Torregrossa and Taylor 2016).

Altogether, the occipital cortex might play an important role in behaviours important for gambling, including craving evoked by cues. It remains to be seen however whether non-invasive neuromodulation targeting the occipital cortex can engage anatomically or functionally connected networks that are relevant to GD to alleviate symptoms.

6.1.4 Cerebellum in gambling disorder

6.1.4.1 Cerebellar substrates and links with depressive symptoms

There is not much evidence showing associations between cerebellar substrates and depression in GD. This might be due to studies excluding patients with GD and comorbid mood disorders. However, it seems pertinent to include such patients, since this is representative of the GD population. As such, the lifetime prevalence of any comorbid mood disorder is 55.6%, 38.6% for MDD and Persistent Depressive Disorder, as well as 17.0% for Bipolar Disorder (Kessler et al. 2008). Interestingly, mood disorders are often present before the onset of GD (i.e., 65.1% of the time for any comorbid mood disorder, 73.5% for MDD/Persistent Depressive Disorder as well as 46.3% for Bipolar Disorder (Kessler et al. 2008). Hence, it might be relevant to consider mood disorders as potential risk factors for GD and to examine substrates of patients with such comorbidities.

There is a line of evidence demonstrating the involvement of the cerebellum in mood disorders (Lupo et al. 2019), which may extend to GD with these comorbidities. For instance, studies found weaker cerebellar rs-FC in patients with mood disorders as compared to healthy individuals (Gong et al. 2020). Studies have also demonstrated smaller gray and white matter volumes of the cerebellum in patients as compared to healthy individuals (Peng et al. 2011; Redlich et al. 2014). In addition, PET studies showed that patients display higher cerebellar glucose metabolism in comparison to healthy individuals, which might be compensatory for decreased metabolism of insular and limbic structures (Su et al. 2014). Furthermore, cerebellar lesions have been associated with mood-related psychiatric symptoms including hypomania and mania (Lupo et al. 2019).

Importantly, cerebellar substrates are associated with depressive symptoms. For example, lower gray matter volume of 13 cerebellar regions were negatively correlated with greater depressive symptoms (scores on the BDI) in patients with MDD (Xu et al. 2017). In addition, a recent study assessing the entire brain found that smaller bilateral cerebellar gray matter volume was negatively correlated with greater anhedonia severity (anhedonia subscores on the BDI) across 175 patients with Opioid Use Disorder, Cocaine Use Disorder, Borderline Personality Disorder, MDD, and Schizophrenia (Schaub et al. 2021). The same study also found a negative correlation between larger anhedonia severity (anhedonia subscores on the Scale for the Assessment of Negative Symptoms) and lesser bilateral cerebellar gray matter volume across 114 patients with MDD, Schizophrenia and first-episode psychosis. These findings support recent dimensional efforts to treat symptoms regardless of the psychiatric disorder, since many disorders share similar neural substrates and symptoms (this will be discussed in a later section). All things considered, the cerebellum might be a key player for depressive symptoms. It may thus be worth targeting this region to alleviate these symptoms in GD. The following sections will discuss how treatments can target and modulate cerebellar substrates.

6.1.4.2 Cerebellum: treatment target?

6.1.4.2.1 Psychotherapy

There are no data showing that behavioural treatments can modulate cerebellar substrates in patients with GD. However, there is a small line of recent evidence that they can do so in patients with Internet Addiction Disorder, which might have important implications for GD. One study used a data-driven machine learning technique called support vector machine modelling to investigate whole-brain rs-FC (Wang et al. 2021). More specifically, the authors created a support vector classification model to classify patients as compared to healthy individuals (i.e., based on their rs-FC) as well as a support vector regression model (i.e., changes in rs-FC) to measure the efficacy of 8 CBT sessions. Both models were successful at classifying patients as well as predicting improvements in symptoms. Interestingly, rs-FC of the cerebellum was the second most important contributor (behind the

superior frontal cortex) to the support vector classification model, and it was the top predictor for the support vector regression model.

This is in line with another study that used a similar approach, in which cue-induced BOLD activity of the cerebellum contributed to the identification of patients with Internet Gaming Disorder and predicted clinical improvements from a behavioural treatment that aimed to reduce craving (Wang et al. 2020). These studies are important since they highlight the pertinence of using a data-driven approach to explore for substrates across the whole brain and that treatments can target such symptoms. Of course, it will be important to conduct replication studies and to test this in patients with GD as well.

6.1.4.2.2 Pharmacological treatments

In line with psychotherapy literature, not much is known regarding the effects of pharmacotherapy in cerebellar functioning in SRADs, including GD. There is some evidence, though that they can alter cerebellar function. For instance, one study showed that former heroin users who underwent methadone replacement maintenance therapy displayed higher cerebellar heroin-related cue-induced BOLD activity as compared to healthy individuals. This suggests that the cerebellum is important for resisting craving and may help prevent relapse since patients did not report increased craving in response to the cues (Tabatabaei-Jafari et al. 2014). In addition, another study found that KB220Z™ decreased cerebellar BOLD resting state activity in heroin users as compared to a placebo (Blum et al. 2015).

6.1.4.2.3 Non-invasive neuromodulation

There are no studies that used non-invasive neuromodulation to target the cerebellum in SRADs. It is only recently that studies have targeted the cerebellum using non-invasive neuromodulation. Up to date, there is some evidence that tDCS targeting the cerebellum can improve motor symptoms in neurological diseases such as Parkinson's disease (Ferrucci et al. 2016; Workman et al. 2020). Two tDCS studies targeted the cerebellum in patients with psychiatric disorders. The first study delivered tDCS over the PFC and cerebellum (anode over the left supraorbital area and cathode over the cerebellum) and showed a slight but non-significant reduction

in depressive symptoms (Ho et al. 2014). The second study demonstrated that tDCS delivered over the PFC (anode over the left DLPFC and cathode over the right supraorbital area) reduced BOLD activity of the cerebellum while patients with Schizophrenia carried out a working memory task (Orlov et al. 2017). However, the potential clinical significance was unclear. Hence, more studies are needed to further our understanding.

There is a line of evidence that rTMS targeting the cerebellum can alleviate symptoms in patients with Schizophrenia. More specifically, studies investigated whether non-invasive neuromodulation could relieve negative symptoms, such as anhedonia and alogia. These symptoms are important to alleviate since they contribute greatly to the morbidity of Schizophrenia, and they are often resistant to medications (American Psychiatric Association, 2013). In addition, the cerebellum is thought to play an important role in the neurobiology of Schizophrenia (Ding et al. 2019). Hence, studies investigated whether delivering non-invasive neuromodulation over the cerebellum can negative symptoms, among others. Most studies found non-invasive neuromodulation to be beneficial. Seven sham-controlled studies found that rTMS (mainly iTBS) delivered to the cerebellum alleviated negative and/or depressive symptoms in patients with Schizophrenia (Zhu et al. 2021; Brady et al. 2019; Basavaraju et al. 2020; Garg et al. 2016; Garg et al. 2013; Demirtas-Tatlidede et al. 2010; Tikka et al. 2015). Two of these studies also provided potential mechanistic insights. One demonstrated that the reduction in symptom severity was negatively correlated with increased iTBS-induced functional connectivity of a fronto-cerebellar network (Brady et al. 2019). In addition, another study found that improvement in symptoms was positively correlated with rTMS-induced reductions in frontal and temporal gamma spectral power (resting state EEG activity) (Tikka et al. 2015). However, two rTMS studies did not find differences between active and sham conditions on symptoms (negative symptoms, depressive symptoms, cognitive symptoms, etc.) (Chauhan et al. 2021; Basavaraju et al. 2021). The authors propose that improving stimulation protocols (e.g., more accurate targeting of the cerebellum, longer treatment duration) might be needed.

Future work will surely refine such protocols. Nevertheless, this line of research has shown promise for cerebellar non-invasive neuromodulation to modulate emotional processes, which may also be useful for other disorders such as mood disorders and GD with these comorbidities.

So far, we have explored the potential importance of the IFG, occipital cortex and cerebellum for the neurobiology of GD. We also demonstrated that treatments, including non-invasive neuromodulation, can modulate their functioning. The following sections will discuss how neuroimaging could be used to inform non-invasive neuromodulation approaches.

6.2. Neuroimaging as a tool to inform non-invasive neuromodulation techniques

6.2.1 Identification of the target region/circuit

Neuroimaging could help identify brain targets for non-invasive neuromodulation to treat patients with GD. High frequency rTMS targeting the left DLPFC is one of the protocols used to treat depressive symptoms in patients with medication resistant MDD. Interestingly, there is a line of evidence that DLPFC target locations whose rs-FC is the most anticorrelated with the subgenual cingulate cortex are associated with the best clinical outcomes (Fox et al. 2012). Not only did this study help uncover a possible rTMS antidepressant mechanism, but it also found a way to potentially optimize clinical response. This approach has helped advance the field, as the DLPFC was previously identified by moving 5 cm anterior to the motor cortex (George et al. 1995; Pascual-Leone et al. 1996; O'Reardon et al. 2007; Padberg and George 2009), which often missed the DLPFC (Herwig et al. 2001 Ahdab et al. 2010). Clearly, it seems important to accurately identify and target the treatment area.

Similarly, identifying optimal brain targets relevant for GD should undoubtedly help treat patients. These efforts are quickly needed, as GD is notoriously difficult to treat.

Up till now, rTMS studies mainly targeted the left or right DLPFC in GD, whereas tDCS mostly targeted the bilateral DLPFC (anodal over the right DLPFC, cathodal over the left DLPFC) (Zucchella et al. 2020; Salatino et al. 2021). This is coherent with the firmly established role of the DLPFC in addiction-related cognitive functions (e.g., motivation, inhibition) and top-down control over reward-related regions (e.g., ventral striatum) (Goldstein and Volkow 2011). The majority of these studies demonstrated that non-invasive neuromodulation can decrease gambling behaviours and craving. However, the heterogeneity of the methods (e.g., stimulation protocols) prevented a recent systematic review from making sound conclusions (Zucchella et al. 2020).

Given the complexity and heterogeneity of GD, it might be worth considering other sites, as discussed in the previous section. Rather than consider a “one size fits all” (i.e., same target for each patient) approach, should scientists consider individualizing non-invasive neuromodulation treatments? Considering that patients with GD have many comorbidities, scientists have recently proposed conceptualizing GD as a “Gambling Dual Disorder” (Szerman et al. 2020). This would likely have important implications for treatment approaches, which could be tailored to GD patients and their comorbidities. This is in line with another study that recently suggested treating patients based on their comorbidities and GD severity (e.g., combining naltrexone and CBT for GD patients with comorbid Alcohol Use Disorder) (Potenza et al. 2019). Likewise, scientists have proposed treating patients based on their cognitive subtypes (e.g., based on impulsivity levels) (Verdejo-Garcia et al. 2019).

Hence, it seems that the SRAD field is leaning towards precision medicine that is based on neuroscientific evidence. The results from this thesis suggest that neuroimaging could be used in conjunction with non-invasive neuromodulation to selectively modulate a clinically relevant circuit. This could be accomplished by testing for correlations between neural substrates and cognitive/clinical symptoms (e.g., impulsivity, depressive scores). This has been demonstrated in other

psychiatric disorders. For instance, a data-driven study used a whole-brain approach to assess substrates of negative symptoms in patients with Schizophrenia (Brady et al. 2019). They found that higher negative symptoms were negatively correlated with weaker rs-FC of between the right DLPFC and the cerebellar midline. The investigators then tested an rTMS regimen in an independent cohort of patients. Patients underwent rs-FC scanning before and after the treatment. They were randomized to receive iTBS or sham twice a day for 5 days over the cerebellar midline. Results showed that iTBS strengthened functional connectivity of the fronto-cerebellar circuit which was negatively correlated with decreased severity of negative symptoms.

So far, this section discussed how neuroimaging could be used to inform the non-invasive neuromodulation field. Another approach that might be worth considering is the patient's anatomical characteristics.

6.2.2 Consideration of potential anatomical influences and how they can optimize "response" to non-invasive neuromodulation

Everyone has a particular brain and cranial anatomy that might influence response to non-invasive neuromodulation. There is some evidence that anatomical factors, including brain morphometry and white matter integrity, can influence non-invasive neuromodulation -induced effects on brain function in patients with SRADs. These studies were conducted using tDCS or rTMS. Firstly, morphometry of the stimulation site can influence response to tDCS and rTMS. As demonstrated in this thesis, larger DLPFCs (volume, thickness) were associated with greater tDCS-induced elevations on fronto-parietal rs-FC and frontal GABA level in patients with GD. In line with this work, larger volume of the left ventromedial prefrontal cortex (TMS target site) was positively correlated with greater rTMS-induced effects on fronto-striatal BOLD activity in patients with Cocaine Use Disorder (Kearney-Ramos et al. 2018). In the same work, there was also a positive correlation between the same rTMS-induced effects and white matter integrity of a fronto-striatal circuit.

In another work, higher left ventromedial prefrontal cortex volume (cTBS target location) was positively correlated with the greater change in alcohol cue-related functional connectivity of a fronto-striatal circuit after real as compared to sham cTBS (Hanlon et al. 2019). Additionally, this work found positive correlations between the cTBS-induced effects and white matter integrity of a fronto-striatal circuit. Furthermore, the authors investigated the influence of the distance between the scalp to the cortex (scalp-to-cortex distance). The rationale behind this is that the strength of the magnetic or electric field declines exponentially as the distance between the targeted region on the scalp and the cortical tissue is increased (i.e., about $1/r^3$; where r refers to the distance) (Summers and Hanlon 2017). The required non-invasive neuromodulation dosage is thus associated with the individual's scalp-to-cortex distance. The authors reported that this distance was positively correlated with the cTBS-induced effects, which was stronger than the associations with gray matter volume and structural integrity. Interestingly, all 3 anatomical characteristics accounted for more than 50% of the variance in cTBS-induced decreases on alcohol-related cue-reactivity. To help further the field, the authors invented an open access tool that measures such distances (Summers and Hanlon 2017).

Taken together, neuroimaging might help enhance response to non-invasive neuromodulation. It may be worth considering the above discussed anatomical factors when designing clinical trials. The potential influence of other anatomical factors could also be assessed (e.g., cerebrospinal fluid, which is highly conductive). Ultimately, non-invasive neuromodulation techniques could be tailored to patients, based on such factors. Patients with impaired structure or functioning of targeted circuits, such as SRADs, might need special non-invasive neuromodulation dosages. Indeed, a recently published study in patients with Alcohol Use Disorder reported smaller gray matter volumes of rTMS-targeted regions (including the left DLPFC) compared to healthy individuals, suggesting that these patients might require higher doses to adequately modulate substrates of interests (McCalley and Hanlon 2021). Another factor that might influence non-invasive neuromodulation response is the state of the patient.

6.2.3 Consideration of potential brain state influences and how they can optimize "response" to non-invasive neuromodulation

Non-invasive neuromodulation effects can be state dependent in patients with psychiatric disorders (Herrera-Melendez et al. 2020; Schiena et al. 2020). State dependency is a phenomenon where the response of a system (e.g., the brain) to a treatment (e.g., non-invasive neuromodulation) is influenced by both the internal state of the system (e.g., brain *activity*) and the properties of the treatment (e.g., tDCS parameters) (Dubreuil-Vall et al. 2021). Hence, it is likely important for studies to consider controlling the patient's state, whether it be before, during or after stimulation, to reduce response variabilities and optimize therapeutic effects.

One of the current unanswered questions in the SRAD/non-invasive neuromodulation field is whether the patient should be sated (e.g., allowed to engage in the addictive behaviour prior to or during the treatment) or abstinent (e.g., not allowed to engage in the addictive behaviour over a certain period before the treatment). A recent trend in non-invasive neuromodulation studies is to expose patients to cue-reactivity tasks before or during stimulation to help non-invasive neuromodulation inhibit an "activated" craving circuit in the aim of helping patients resist craving (Steele and Maxwell 2021). Additionally, it might be worth considering whether the patient is still engaged in the addictive behaviour, is abstinent, or is motivated to quit, as these factors will likely impact non-invasive neuromodulation effects (Ekhtiari et al. 2019). Also, motivation might also be worth considering. For instance, as previously discussed, a study reported that patients with greater motivation to quit had greater tDCS-induced reductions in cigarette consumption (Vitor de Souza Brangioni et al. 2018).

Furthermore, scientists could consider neuroimaging-verified neural states (e.g., using fMRI, MRS, or EEG) to predict best responders (e.g., pathological physiological signatures). For instance, a recently published paper reported that patients with ADHD and higher pathological EEG signatures (large N200 and small P300, i.e., event-related potentials related to executive functions) had greater tDCS-

induced improvement of cognitive performance (Dubreuil-Vall et al. 2021). Hence, scientists could consider specific brain activity correlates that predict responses to non-invasive neuromodulation and adjust protocols therefore to optimize response to treatment. Lastly, it might be worth considering brain-state dependent stimulation (Bergmann 2018). The rationale behind this is that the brain is a dynamic system. Hence, technological advances such as concurrent neuroimaging and real-time signal analysis could be used to activate or adjust the intervention when needed (also known as a closed loop system) (Bergmann 2018).

Taken together, neuroimaging seems promising to optimize non-invasive neuromodulation responses. Although more research is needed, it has the potential to help answer important questions of how, where and when the brain should be stimulated to maximize clinical outcomes.

6.3. Limitations and strengths

Several limitations and strengths should be acknowledged. Firstly, the studies in this thesis all had small sample sizes (but they were adequate based on calculation), which limits their statistical power. These studies will nevertheless help future studies (i.e., RCTs) calculate sufficient sample sizes. In addition, the sample was representative of the GD population (Kessler et al. 2008). For instance, some had comorbidities such as tobacco smoking, some took medications for sleep disorders, depression, and/or anxiety (although they were stable for at least three months prior to their participation). Thus, to some individuals, our sample might be heterogeneous, but to others it might not be so. For example, we excluded patients under 20 years of age, whose brain maturation is not complete, although it is well-known that GD can be present in younger age groups). This is nevertheless an important direction, as comorbidities are frequent and many studies in the literature excluded patients who had them.

Furthermore, our studies used validated and reliable measures, however, most were self-reported and therefore potentially biased due to subjectivity. It will therefore be important for future work to consider using task-based methods to measure clinical

(e.g., craving) and cognitive (e.g., impulsivity) data to enhance our understanding of substrates.

There are also some important limitations to consider regarding the rs-FC findings (Bijsterbosch et al. 2017). For instance, the state of the individual, such as arousal, can vary dramatically during a scanning session and influence rs-FC. Although we made sure subjects did not fall asleep, future work could be strengthened by including in-scanner eye-trackers (if budget permits). Additionally, these patients were treatment-seekers and several of them were taking medications (mostly antidepressants and/or anxiolytics, but some took stimulants). Although this likely reflects the population, their potential impact on morphometry and rs-FC should be explored in future work.

Moreover, the clinical significance of all 4 studies remains unclear. For example, it is uncertain whether the IFG, occipital cortex and cerebellum are relevant to all patients with GD or certain subgroups (with high impulsivity, risk-taking, depression, etc.). Yet, both studies used whole-brain approaches and proposed the potential importance of such regions, which may not have otherwise been considered, as they are not “classic” reward-related regions. Concerning the tDCS studies, it is unclear whether the modulation of substrates persisted beyond the stimulation period and whether they could potentially improve symptoms (and if so, which ones?). However, similar to the SUD field, it is likely that several tDCS sessions are needed to treat symptoms (Ekhtiari et al. 2019). This should be thus investigated in future work.

Altogether, this thesis uncovered potential substrates that may serve as treatment targets in GD patients with comorbid depressive disorders and Tobacco Use Disorder. Further, this thesis supported the individualization of non-invasive neuromodulation approaches by considering anatomical factors to identify best responders to such treatments. There are several approaches that may be considered to advance the field.

6.4. Future directions

6.4.1 Optimize/explore treatment approaches

Although tDCS is a promising approach, administering tDCS alone is likely not the "holy grail" treatment, as a multifaceted approach combining several treatments is likely needed to induce long-term alleviation of symptoms (Ekhtiari et al. 2019). Combining non-invasive neuromodulation with pharmacological or behavioural interventions might be worth considering to further boost neuroplasticity, possibly more so than if the interventions were provided alone (Spagnolo et al. 2019). For instance, combining CBT (twice/week for 3 weeks) with four sessions of iTBS over the right DLPFC resulted in greater abstinence rates at 3 months post treatment as compared to those who received sham iTBS with CBT (Dieler et al. 2014). Further, studies should examine tDCS-induced effects on substrates after the treatment, regardless of whether they are proof-of-concept or clinical trials with a greater number of sessions. It will be important to assess whether tDCS effects on clinical and neural outcomes last. In addition, more work is needed to uncover which tDCS parameters are most appropriate for clinical responses, including dose-response studies (Esmaeilpour et al. 2018). Finally, more work is needed to develop better tDCS blinding protocols, particularly for crossover designs, as participants can compare sensations and skin redness across sessions (Fonteneau et al. 2019).

6.4.2 Explore subject-related factors on substrates and treatment outcomes

Future work should assess the influence of patient-related factors on neural substrates, including age and sex, GD severity and duration, as well as medications and comorbidities. Firstly, patients with SRADs can show sex-related differences in brain morphometry (Franklin et al. 2014; Kogachi et al. 2017) and rs-FC (Wetherill et al. 2014; Zhang et al. 2017; Moran-Santa Maria et al. 2018; McCarthy et al. 2019a; Wang et al. 2019). For instance, in patients with Tobacco Use Disorder, men, but not women, displayed larger bilateral parahippocampal volumes, possibly reflecting greater activity during cue-related memory retrieval (Franklin et al. 2014). Additionally, women demonstrated weaker rs-FC in networks associated with cognitive control (e.g., fronto-striatal circuitry) as compared to men, which could help

explain why women have lower success at quitting (McCarthy et al. 2019a). In our studies, we had insufficient statistical power to conduct exploratory analyses on sex, despite our sample consisting of almost 50% women. Sex-related differences should thus be examined in future work, considering that there is a rise in women gambling and there is a paucity of research including them (McCarthy et al. 2019b).

Secondly, healthy individuals display age-related variations in morphometry (Zhao et al. 2019; Irimia 2021) and rs-FC (Varangis et al. 2019; Zonneveld et al. 2019; Jockwitz and Caspers 2021) in regions and networks that are relevant to SRADs. For example, one study found greater age-related reductions in volumes of several areas including frontal, occipital, and temporal regions (Zhao et al. 2019). In addition, another study reported reduced rs-FC strength of various networks, such as the ventral attention, default mode, and sensorimotor networks as well as increased rs-FC strength of occipital networks (Zonneveld et al. 2019). Further, age is likely worth considering for non-invasive neuromodulation protocols, especially since greater age is associated with larger cerebrospinal fluid volumes (which are highly conductive) (Thomas et al. 2018).

Thirdly, GD duration and severity can influence neural substrates. For example, in a recent study, GD duration (months) was positively correlated with rs-FC of insulo-frontal and insulo-temporo-parietal circuits (Tsurumi et al. 2020). The authors proposed that these results might reflect dopamine-mediated adaptations. However, more work is needed to better understand the relationship between rs-FC and GD duration at large, given that the gambling form of the patients in this study was Pachinko, which is a gaming machine that is specific to Japan with similarities to pinball and slot machines.

Additionally, another recent study reported a positive correlation between GD severity and rs-FC of an ICA-derived cerebellar network (Piccoli et al. 2020). Likewise, these factors are likely worth considering for treatment outcomes, as they are associated with different characteristics. For instance, moderate and high GD

severity were associated with greater financial losses, lower quality of life, larger tobacco consumption and higher anxiety and depression, as compared to lower GD severity (Grant et al. 2017). Also, greater GD duration is negatively correlated with lower quality of life (Medeiros et al. 2017). One might therefore purport that treatment response may differ between patients with different GD severities and durations, as patients with greater GD severity (e.g., bankruptcy) are more likely to seek help than those with lesser severity (Suurvali et al. 2008).

Furthermore, medications can influence neural substrates (as discussed in a previous section) and should be taken into consideration for non-invasive neuromodulation outcomes (McLaren et al. 2018). In addition, comorbidities should be considered. It will be likely worth tailoring non-invasive neuromodulation interventions to patients based on their substrates or symptoms, as discussed in a previous section. This is in line with the trend towards person-specific psychiatry. As proposed over 50 years ago, scientists should keep in mind: "*What* treatment, by *whom*, is most effective for *this* individual with *that* specific problem, and under *which* set of circumstances?" (Paul 1967). The next section will describe the effects of comorbidities on neural substrates.

6.4.3 Examine substrates in gambling disorder patients with comorbidities and explore gambling form preferences

As previously discussed, future work should assess substrates in GD patients that have comorbidities, as it represents the actual GD population (Potenza et al. 2019). For instance, 96% of patients with GD are estimated to have at least one comorbid psychiatric disorder (Kessler et al. 2008). The 18 patients recruited in this thesis displayed several comorbidities. These included Tobacco Use Disorder (n = 9) and depressive symptoms (mild n = 7; moderate n = 6; severe n = 1). Interestingly, patients also reported compulsive shopping (n = 7), compulsive exercise (n = 1), hypersexuality (n = 7), Intermittent Explosive Disorder (n = 5), kleptomania (n = 7), pyromania (n = 2) and trichotillomania (n = 1). The high heterogeneity in our sample supports the literature. Interestingly, many of the comorbid disorders are part of the Disruptive, Impulse-Control and Conduct Disorders section of the DSM-5 (American

Psychiatric Association 2013), in which GD was in the previous edition. Hence, it might be worth considering subgrouping GD patients based on their comorbidities to better understand the substrates and treat the disorder.

Furthermore, it might be interesting to explore whether neural substrates differ based on preferred gambling form(s). Indeed, electronic gaming machines (including slot machines, video lottery terminals, and video poker) are thought to be the most addictive form of gambling, where they are associated with both more rapid onset of GD and greater GD severity (Breen et al. 2002; Dowling et al. 2005; MacLaren et al. 2016). Of the 18 recruited patients in this thesis, slot machines were the most preferred gambling form, where 8 patients gambled using slot machines only. Two patients gambled using solely lottery tickets or scratch cards, 3 only gambled with poker, and the rest (n = 5) gambled with multiple gambling forms, including slot machines, lottery tickets, roulette, blackjack, and/or sports betting.

6.4.4 Consider potential translation of findings to other psychiatric disorders, based on shared substrates and symptoms with other disorders (Research Domain Criteria)

Given that there is high overlap of symptoms and substrates between GD and other disorders, it might be worth assessing whether the results from this thesis translate to other psychiatric disorders. Our findings might particularly translate to those with elevated impulsivity and risk-taking (e.g., impulse-control disorders, SUDs), as well as comorbid mood disorders (e.g., SUDs). Future work could consider using the Research Domain Criteria to help answer these questions.

Launched by the U.S. National Institutes of Mental Health in 2009, the Research Domain Criteria project (RDoC) is a framework that does not rely on disorder-based categories (National Institute of Mental Health 2021; Incel et al. 2010). It aims to further our understanding of the mechanisms of both healthy and unhealthy brains across the lifespan to inform diagnostic and treatment strategies. Traditionally, psychiatric disorders are diagnosed based on the number and type of symptoms in addition to important impairment or distress (American Psychiatric Association 2013;

World Health Organization 2018). However, this approach has some consequences that limit our understanding of the disorders.

Firstly, research can produce heterogeneous findings, which makes it challenging for scientists to understand the neural substrates of a disorder (e.g., 2 patients can be diagnosed with the same disorder but have little or no common symptoms; this especially pertains to GD as only 4 of 9 criteria are needed for a diagnosis by the DSM-5). Secondly, to reduce heterogeneity, scientists often include patients with "pure" disorders (with little or no comorbidities). However, this lack of variation may limit our understanding of the substrates. As previously discussed, patients often have comorbid symptoms, including GD, which questions considering "one" disorder and not dual disorders or comorbidities. For instance, recent work demonstrated common emotional processing substrates (PFC, striatum, etc.) across several psychiatric disorders, including SUDs and mood disorders (McTeague et al. 2020). Furthermore, another approach that the RDoC recommends is to consider dimensional conceptualizations to better understand the entire spectrum of psychiatric disorders (e.g., including participants that display symptoms but do not meet the number required for a diagnosis). Separating patients into different groups based on their symptoms could prevent our understanding of the disorder, and potentially limit prevention and treatment strategies. The RDoC framework is implemented as a matrix, which comprises 6 domains of human functioning: 1) Negative Valence; 2) Positive Valence; 3) Cognitive Systems; 4) Systems for Social Processes; 5) Arousal/Regulatory Systems; 6) Sensorimotor Systems. These domains have a combined total of 39 constructs (behavioural elements, e.g., cognitive control and attention for cognitive systems) which are studied across both abnormal and normal functioning using various methods including neuroimaging. There is a recent Delphi consensus study by a team of 44 experts that proposed 7 primary constructs for SRADs (Yücel et al. 2019): 1) action selection, 2) expectancy, 3) habit, 4) reward learning and 5) reward valuation (all from the Positive Valence System), as well as 6) response selection (from the Cognitive Control System) and 7) compulsivity (a new proposed construct). Although these primary constructs

appear important, it is unclear to which extent they translate to all SRADs, such as those with differing comorbidities. It might thus be important for future work to consider secondary constructs which could represent comorbidities.

6.4.5 Investigate the impact of the COVID-19 pandemic on gambling

It might be worth investigating the impact of the COVID-19 pandemic on gambling, given the closure of non-essential businesses (e.g., casinos) during the pandemic. Although preliminary, there is some evidence for a shifting of gambling and other addictive behaviours. For instance, most gamblers reported decreased gambling online activity during the pandemic lockdown, but they increased their substance (e.g., alcohol, cannabis, tobacco) use (Xuereb et al. 2021). Additionally, in the same study, 15% of casino gamblers migrated to online gambling and these individuals had greater levels of problem gambling. Hence, such individuals might be considered vulnerable to GD.

Furthermore, another study reported increased craving and engagement in addictive behaviours (alcohol, gambling, tobacco, etc.) in individuals who engaged in such behaviours (including those who recovered from them) prior to the pandemic (Bonny-Noach and Gold 2021). Altogether, these findings suggest a need for increased surveillance of potential SRAD development and relapses in addition to creation of measures to prevent such occurrences.

Conclusion

To conclude, this thesis contributed to better understanding GD brain substrates and tDCS-induced effects on such substrates. Future work could use Diffusion Tensor Imaging and PET to measure white matter integrity and dopamine levels, respectively, which are relevant to GD. To improve our comprehension of tDCS effects, studies could also use MRS to measure other correlates that are relevant to SRADs such as inflammation and oxidative stress (Kohut and Kaufman 2021). Future work could also use rs-fMRI to measure effective connectivity (e.g., in which direction the tDCS-targeted region influences the functional connectivity of other regions (Bijsterbosch et al. 2017)). Further, it will It is likely pertinent to consider state-dependent and trait-stable symptoms as well as cognitive processes to understand substrates. For example, certain measures such as craving and risk-taking can be time sensitive or “dynamic”, i.e., varying day to day or within the day itself (e.g., Tiffany and Wray 2012; Byrne and Murray 2017; Treloar Padovano et al. 2018; Maclean et al 2018). How their variations associate with rs-FC and other time-sensitive substrates are worthy of further study. Finally, it will likely be important to use multimodal approaches, such as combining fMRI and electroencephalography to develop biomarkers for SRADs and to gain a better understanding of substrates (Ekhtiari et al. 2019; Kohut and Kaufman 2021).

Appendix I: Cognitive functions in substance-related and addictive disorders

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Abstract

Despite the availability of treatments such as medications and cognitive behavioural therapy, relapse remains high in substance-related and addictive disorders. Cognitive functions, including cognitive biases and executive functions, are significant predictors of relapse. Alleviating cognitive deficits is therefore promising to suppress craving and decrease relapse. Transcranial current stimulation holds potential to improve cognitive functioning in these patients. This chapter provides an overview of the use of transcranial current stimulation to modulate cognitive functions in substance-related and addictive disorders. We show that transcranial current stimulation can decrease cognitive biases and improve executive functions across various substance-related and addictive disorders, especially regarding decision-making and when targeting the dorsolateral prefrontal cortex bilaterally. We also discuss the relationship between cognitive functions and several processes, such as craving, mood, and stress, which should be taken into account when developing future transcranial current stimulation protocols. Lastly, we provide suggestions as to how future studies could be improved to better treat patients with these debilitating disorders.

Keywords: substance-related and addictive disorders, executive functions, cognitive bias, dorsolateral prefrontal cortex

1. Introduction

Substance-related and addictive disorders (SRADs), including alcohol, cannabis, gambling, and stimulant use disorders, are characterized by maladaptive behaviour or dysfunctional use of a substance that leads to clinically distressing consequences (e.g., craving, health issues, interference with work, school or personal life) [1]. SRADs are difficult to treat and relapse remains a big issue despite available pharmacological and behavioural treatments. Crucially, cognitive deficits (e.g., cognitive biases, deficits in executive functions) can predict relapse [2]. Hence, improving cognitive functions is a promising therapeutic option for dealing with craving and relapse [2]. Cognitive deficits can be present before the onset of SRADs and worsen with chronicity [3]. Yet, not all patients with SRADs present the same cognitive profile, as they can vary across diagnoses and as a function of comorbidities [2]. More specifically, a meta-analysis found that patients with alcohol and stimulant use disorders particularly present impaired cognitive flexibility; patients with cannabis and 3,4-methylenedioxy-methamphetamine (MDMA) use disorders predominantly display impairments in complex planning and processing speed; patients with opioid use disorder mostly demonstrate reasoning impairments, and patients with cannabis and methamphetamine use disorders mainly show memory deficits [4].

Within this context, transcranial current stimulation (tCS) over the dorsolateral prefrontal cortex (DLPFC) has been successfully used to strengthen cognitive functions [5-14] and help patients resist craving and avoid relapse. Given such evidence, an overview of which cognitive functions have been successfully improved in patients with SRADs can inform clinical practice and help develop new interventions. Hence, this chapter reviews studies that examined tCS-induced effects on cognitive functions relevant to SRADs, namely cognitive bias and executive functions. The relationship between cognitive functions and craving, mood, and stress is also discussed. All included studies are sham-controlled,

randomized, blinded, and used transcranial direct current stimulation, unless otherwise stated (**Table 1**).

Table 1. Transcranial current stimulation can modulate several cognitive functions in substance-related and addictive disorders.

First author, year [ref#]	Design (N)	Addictive disorder	tDCS parameters	Anode placement	Cathode placement	Outcome measure(s)	Findings
Cognitive bias							
Mondino, 2020 [14]	Randomized Double-blind Sham-controlled Crossover (19)	Tobacco	1 session/condition[a] 10Hz, 2mA 30 min	N/A	N/A	Observation of smoking-related and neutral stimuli with eye tracking	↓ amount of time looking at smoking-related pictures
Vanderhasselt, 2020 [5]	Randomized Double-blind Sham-controlled Crossover (37)	Alcohol	1 session/condition 2 mA 20 min	R DLPFC	L DLPFC	Rewarded Go/No Go	↓ reward-triggered approach bias
Claus, 2019 [18]	Randomized Double-blind Sham-controlled 2 x 2 factorial (79)	Alcohol	4 sessions (once a week for 4 consecutive weeks)[a] 2 mA 2 x 10 min	R IFG	L upper arm	Approach-Avoidance-Task	No significant effect
Den Uyl, 2018 [17]	Randomized Double-blind Sham-controlled 2 x 2 factorial (83)	Alcohol	4 sessions over one week[a] 2mA 20 min	L DLPFC	R DLPFC	Visual probe task Implicit Association Task	No significant effect
Shahbabaie, 2018 [6]	Randomized Double-blind Sham-controlled Parallel (90)	Methamphetamine	1 session 2mA 2 x 13 min	L DLPFC	R shoulder or R DLPFC^	Probe detection task	↓ attentional bias toward drug cues
Den Uyl, 2017 [13]	Randomized Double-blind Sham-controlled Parallel (91)	Alcohol	4 sessions over one week[a] 2 mA 20 min	L DLPFC	R DLPFC	Approach avoidance task	↓ approach bias
Den Uyl, 2016 [19]	Randomized Double-blind Sham-controlled 2 x 2 factorial (78)	Alcohol	3 sessions over 3 or 4 days[a] 1 mA 15 min	L DLPFC	R supraorbital area	Approach avoidance task Implicit Association Task	No significant effect
Cognitive flexibility							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Wisconsin Card Sorting Task	↓ perseverative errors ↑ completed categories
Soyata, 2019 [8]	Randomized Triple-blind Sham-controlled Parallel (20)	Gambling	3 every other day sessions 2 mA 20 min	R DLPFC	L DLPFC	Wisconsin Card Sorting Task	↓ perseveration errors

Decision making							
Mondino, 2020 [14]	Randomized Double-blind Sham-controlled Crossover (19)	Tobacco	1 session/condition[a] 10Hz, 2mA 30 min	N/A	N/A	Delay Discounting Task	↓ percent of immediate choices
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Balloon Analog Risk Task	↓ adjusted value ↓ maximum pumping
Soyata, 2019 [8]	Randomized Triple-blind Sham-controlled Parallel (20)	Gambling	3 every other day sessions 2 mA 20 min	R DLPFC	L DLPFC	Iowa Gambling Task	↑ net score
Gorini, 2014 [9]	Randomized Single-blind Sham-controlled Crossover (18)	Cocaine	1 session/condition 1.5 mA 20 min	L/R DLPFC	L/R DLPFC	Game of Dice Task Balloon Analog Risk Task	↓ average of safe bets (anode over L DLPFC) ↑ average of safe bets (anode over R DLPFC) ↓ adjusted average pumps
Fecteau, 2014 [10]	Randomized Quadruple-blind Sham-controlled Crossover (12)	Tobacco	5 daily sessions/condition 2 mA 30 min	R DLPFC	L DLPFC	Ultimatum Game	↑ rejected offers of cigarettes
Pripfl, 2013 [11]	Counterbalanced Sham-controlled Crossover (18)	Tobacco	1 session/condition .45 mA 15 min	L/R DLPFC	L/R DLPFC	Cold Columbia Card Task Hot Columbia Card Task	↓ number of cards chosen in risky gamble (anode L DLPFC/cathode R DLPFC) ↓ number of cards chosen in risky gamble (anode R DLPFC/cathode L DLPFC)
Boggio, 2010 [25]	Randomized Double-blind Sham-controlled Parallel (25)	Cannabis	1 session 2 mA 15 min	L/R DLPFC	L/R DLPFC	Risk Task	↑ choice of more risky prospects
Self-regulation							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Go/No-Go	↓ reaction time ↑ accuracy go trials ↑ accuracy no-go trials
Aronson Fischell, 2020 [29]	Randomized Double-blind Sham-controlled Crossover (15)	Tobacco	1 session/condition 2 mA 25 min	L DLPFC R VMPFC	R VMPFC L DLPFC	Flanker Task	No significant effect
Witkiewitz, 2019 [31]	Randomized Double-blind Sham-controlled Parallel (84)	Alcohol	Variable number of sessions[ab] 2 mA 30 min	R IFG	L upper arm	Stop Signal reaction time task	No significant effect
Lee, 2018 [12]	Open-label Single-arm (15)	Internet Gaming	3 sessions a week for 4 weeks 2 mA 30 min	L DLPFC	R DLPFC	Brief Self Control Scale	↑ self-control
Selective attention							

Xu, 2013 [33]	Counterbalanced Single-blind Sham-controlled Crossover (24)	Tobacco	1 session/condition 2 mA 20 min	L DLPFC	R supraorbital area	Visual attention task	No significant effect
Working memory							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	N-back	↓ response time ↑ accuracy
Aronson Fischell, 2020 [29]	Randomized Double-blind Sham-controlled Crossover (15)	Tobacco	1 session/condition 2 mA 25 min	L DLPFC R VMPFC	R VMPFC L DLPFC	N-back	No significant effect
Overall executive function							
da Silva, 2013 [34]	Randomized Sham-controlled Parallel (13)	Alcohol	One session per week for five weeks 2 mA 20 min	L DLPFC	R supradeltoid area	Frontal Assessment Battery	No significant effect
Klauss, 2014 [35]	Randomized Double-blind Sham-controlled Parallel (33)	Alcohol	2 daily sessions for 5 consecutive days 2 mA 13 min	R DLPFC	L DLPFC	Frontal Assessment Battery	No significant effect

DLPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; VMPFC: ventromedial prefrontal cortex; L: left hemisphere; R: right hemisphere; ↑: increase; ↓: decrease. Some articles appear more than once since they measured more than one cognitive function; [a]some or all subjects received a behavioural intervention as well; [b]subjects participated in a rolling group mindfulness-based relapse prevention while receiving either active or sham tDCS; those in the active and sham groups attended 4.32 and 3.78 sessions, respectively.

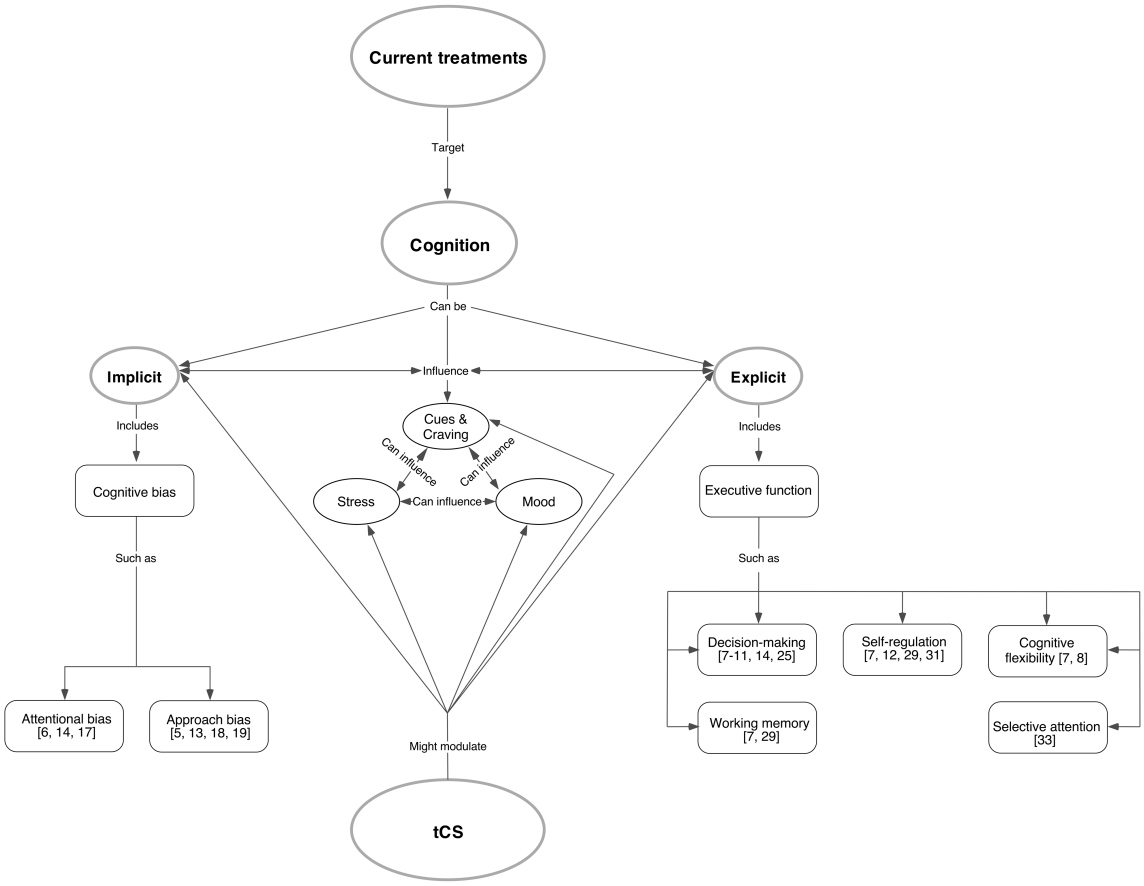
2. tCS effects in cognitive functions in SRADs

Several studies assessed the effects of tCS on cognitive functions in SRADs. These can be divided into two main categories: studies on implicit cognitive functions, e.g., cognitive bias, and studies on explicit cognitive functions, e.g., executive functions (see Figure 1; Table 1).

2.1 tCS effects on cognitive biases in SRADs

Some patients with SRADs are aware that their addictive behaviour is detrimental, yet they still carry it out despite the negative consequences. One way to explain this behaviour is by taking into account implicit cognitive functioning, such as cognitive biases. Cognitive biases are automatic, implicit, and favorable processing of certain stimuli (e.g., external cues) over others [15]. Two major forms are approach bias and attentional bias. Approach bias happens when patients are quicker to approach rather than avoid cues [15]. Attentional bias occurs when patients display biased attention towards cues, which can increase craving [16]. Seven studies assessed the effects of tCS on cognitive biases [5, 6, 13, 14, 17-19] in alcohol and methamphe-

Figure 1. Transcranial current stimulation and current treatments might be used to target implicit as well as explicit cognitive functions in substance-related and addictive disorders. Some other processes might be worth targeting as well, such as craving, mood and stress, since they can influence cognitive functions and vice versa.



tamine users. Four of these studies found significant reductions in cognitive biases when targeting the bilateral DLPFC [5, 6, 13, 14], as well as the DLPFC and shoulder [6]. In particular, two studies found reduced approach biases in alcohol users when placing the anode over the right and cathode over the left DLPFC [5] and vice versa [13]. Also, one of these studies combined tCS with a cognitive bias modification protocol [13]. In addition, one study found decreased attentional biases in tobacco smokers when patients received real transcranial alternating current stimulation

(tACS) paired with attentional bias modification as compared to sham tACS with attentional bias modification training, as shown by decreased time observing smoking-related stimuli measured with an eye tracker [14]. Further, a single study reported decreased attentional bias towards drug cues in abstinent, treatment-seeking patients with methamphetamine use disorder [6]. Patients performed a probe detection task before and after they received two 13-minute tCS sessions. Patients were randomly assigned to one of six groups with different electrode montages: 1) anode over the left DLPFC, cathode over the right shoulder; 2) anode over the right DLPFC, cathode over the left shoulder; 3) anode over the left DLPFC, cathode over the right supraorbital ridge; 4) anode over the right DLPFC, cathode over the left supraorbital ridge; 5) anode over the left DLPFC, cathode over the right DLPFC. Sham condition consisted of electrodes over the right and left DLPFC. Of these, two groups displayed reduced attentional bias towards cues as measured by reaction times, that is, one group receiving anodal and cathodal tDCS over the left and right DLPFC, respectively, and one group receiving anodal and cathodal tDCS over the left DLPFC and the shoulder, respectively.

2.2 tCS effects on executive functions in SRADs

Higher order cognitive functions, such as executive functions, are believed to be impaired in SRADs [2, 3]. Some researchers purport that patients with SRADs have an imbalance between implicit and explicit processes, in which executive functions fail to control implicit urges. In line with this, a series of studies attempted to increase cognitive control to reduce addictive behaviour. Several studies have assessed the effects of tCS in SRADs on a wide range of executive functions, such as cognitive flexibility, decision-making, working memory, self-regulation, and selective attention (see Figure 1; Table 1).

Cognitive flexibility, also known as set-shifting, reflects the ability to adapt to different responses or situations [20]. Measuring cognitive flexibility can be a useful marker of cognitive control and possibly compulsivity [21]. Two studies reported improved cognitive flexibility following tCS over the DLPFC (anode over the left, cathode over

the right DLPFC) in patients with methamphetamine use disorder [7] and gambling disorder (anode over the right, cathode over the left DLPFC) [8]. More specifically, patients showed decreased perseveration errors and/or completed categories on the Wisconsin Card Sorting Task [22].

Decision-making encompasses evaluating potential outcomes and selecting the most appropriate option [23]. This ability can be impaired in patients with SRADs, in that they show a tendency to choose immediate rewards (e.g., drug or monetary rewards) despite the possible detrimental consequences [24]. Up to now, six studies examined the effect on decision-making of tCS over the bilateral DLPFC across different SRADs, including cocaine [9], gambling [8], methamphetamine [7], tobacco [10, 11, 14], and cannabis [25] use disorders. Some studies applied the anode and cathode over the right and left DLPFC [8, 10], and vice versa [7], whereas some used both montages [9, 11, 25], and one used tACS to target both DLPFCs [14]. The first six studies reported improvements in various measures of decision-making (e.g., Balloon Analog Risk Task, Iowa Gambling Task, Game of Dice Task, Ultimatum Game, Columbia Card Task, Delay Discounting Task). The last study reported increased risky choices among patients with cannabis use disorder [25]. Nonetheless, this study demonstrated that these patients display different decision-making processes as compared to healthy individuals for the same task [26].

Working memory refers to the ability to store and use short-term information [3, 27] which can influence other processes, such as decision-making. For instance, working memory training decreases delay discounting in patients with stimulant use disorder [28]. Two studies evaluated the effects of tCS on working memory in patients with SRADs. The first one reported decreased response time and increased accuracy on the N-Back Task by applying tCS over the DLPFC (anode over the left and cathode over the right DLPFC) in methamphetamine use disorder [7]. The second study (which placed the electrodes over the ventromedial PFC and the DLPFC with reversed polarity) did not find significant effects on the N-Back Task [29].

Self-regulation reflects the ability to maintain ideal motivational, emotional, and cognitive arousal, including inhibition and self-control [27]. Inhibition is the ability to control actions, thoughts, behaviours, and/or emotions to overcome internal (e.g., craving) or external (e.g., cue-induced) desire [27]. Self-control reflects the ability to resist temptations and hastiness [27]. Low self-control is a hallmark of SRADs [1] as it may predispose individuals to the inability to control, reduce, or stop the addictive behaviour [30]. Four studies evaluated tCS-induced effects on response inhibition [7, 29, 31] and self-control [12]. Regarding response inhibition, one study applied tCS over the DLPFC (anode over the left DLPFC, cathode over the right DLPFC) and reported significantly increased accuracy of trials and decreased reaction time on the Go/No-Go task [7]. The other two studies were conducted in patients with tobacco use disorder [29] and heavy drinkers (98.9% of individuals displayed alcohol use disorder) [31] but they did not report significant tCS-induced effects. To note, one of these studies combined tCS with mindfulness-based relapse prevention [31]. The effects of tCS on self-control was evaluated in a prospective study on patients with internet gaming disorder [12]. This was a single-arm, open-label study in which patients received 12 active tCS sessions (anode over the left and cathode over the right DLPFC) three times a week for four weeks. Patients displayed increased self-control, which correlated with decreased severity and time playing games as assessed by the Brief Self Control Scale [12]. Interestingly, the tCS regimen was followed by a partial alleviation of the asymmetry of glucose metabolism between the two DLPFCs. Although speculative, this may reflect a better communication between the two DLPFCs, which could lead to increased self-control. Despite the promising results, randomized, sham-controlled studies are necessary to draw further conclusions.

Selective attention is demonstrated by the ability to maintain attentional focus on the environment [27]. This function is closely related to working memory and attentional biases, since both require holding attention for some time [15, 27]. In SRADs, selective attention predicts the motivation to engage in treatment [32]. Work by Xu

and collaborators [33] found no effect of tCS on selective attention in patients with tobacco use disorder. The study used anodal and cathodal tCS over the left DLPFC and the right supraorbital area, respectively. The authors discussed that this may be due to spurious factors, such as the fact that patients were abstinent overnight, which might influence tCS-induced effects on cortical excitability.

Two studies evaluated the effects of tCS on overall executive functions [34, 35], as assessed by the Frontal Assessment Battery, in patients with alcohol use disorder. Although the studies used different montages, neither of them found significant effects. Nevertheless, some limitations of the studies should be mentioned. For one, one study presented differences in the baseline amount of drinking between the active and sham groups [34]. Moreover, both studies had small sample sizes, which may reflect a lack of statistical power.

2.3 tCS effects on craving, mood, and stress in SRADs

Craving, mood, and stress also play a major role in SRADs. They can influence cognition and can be modulated by tCS [36] (see **Figure 1**).

Craving is a complex process where individuals display a powerful urge or desire for a substance or an addictive behaviour (e.g., gambling, internet gaming) [1]. Craving can be triggered by external cues (e.g., a person, a place, or an object), as well as internal signals, such as mood or stress [37]. It is believed to play a central role in SRADs and constitutes one of the diagnostic criteria in the DSM-5 [1]. Several clinical studies confirmed that tCS over the bilateral DLPFC can decrease craving in SRADs (for reviews, see [36, 38]). Yet, it remains to be seen whether this effect is due to a direct impact of the stimulation on craving or to an indirect effect which is secondary to an improvement of cognitive control [2].

Mood can also influence SRADs, since it can reinforce addictive behaviour [39]. For instance, anxious or depressive moods can influence cognitive functions such as self-control or decision-making and trigger craving and relapse. Therefore, improving

mood might be one way to improve cognitive control to resist substances. Some evidence points to the effectiveness of tCS in improving mood in patients with SRADs [33, 40]. Two studies on tobacco use disorder found reduced negative affect following (1) anodal stimulation over the right (but not left) DLPFC and cathodal stimulation over the right DLPFC [40] and (2) anodal stimulation over the left DLPFC and cathodal stimulation over the right supraorbital area [33]. In both studies, there were differences neither in craving, nor in cigarette consumption. To note, patients were abstinent for at least six [40] or ten [33] hours, possibly suggesting the pertinence of testing in sated patients. Further, a preliminary study reported that tCS increased the perception of the quality of life in patients with online gaming disorder [12] (the details of this study are described in Table 1 as well as in a previous section about self-control).

Stress is a psychological and phenomenological experience accompanied by a specific physiological response [41]. Stress is purported to play a role in different stages of SRADs, from the initiation of the addictive behaviour to its relapse [41]. Both stress and addictive disorders are thought to share common neurophysiology, including a disrupted hypothalamic-pituitary-adrenal axis, as well as disrupted cognitive functions (e.g., selective attention, decision-making). In turn, both stress and addictive disorders may influence mood and cue reactivity, thereby increasing craving and probability of relapse. Furthermore, withdrawal symptoms themselves can cause stress for the individual. Thus, it is important to provide stress-coping strategies for patients with SRADs. Some evidence indicates that one session of active tCS over the DLPFC (anode over left DLPFC; cathode over right DLPFC), as compared to sham, can prevent a stress response (e.g., cortisol level) and decrease anxiety in healthy individuals that undergo psychosocial stress [42]. It remains to be seen whether tCS may be beneficial to stress reduction also in patients with SRADs.

3. Discussion

Taken together, there are some trends that allow us to observe a general picture. Firstly, targeting the bilateral DLPFC appears to be the most effective tCS approach

[5-10, 12-14], regardless of anode or cathode placement (see Table 1). This might suggest the importance of location and not laterality in SRADs [36], at least for cognitive functions. Secondly, decision-making was the most improved function across a variety of SRADs (tobacco, methamphetamine, gambling, cocaine use disorders, but not cannabis use disorder), which all targeted the bilateral DLPFC. Hence, there appears to be a link between targeting the DLPFCs and ameliorated decision-making. One possible explanation is that tCS modulates the interhemispheric balance between the two DLPFCs that is needed for decision-making functions [43]. It might be interesting for future studies to examine any possible underlying mechanisms (e.g., using fMRI). Also, it might be worth examining whether tCS can modulate other cognitive functions that are impaired across different SRADs (e.g., cognitive flexibility in alcohol and stimulant use disorders, reasoning in opioid use disorder, etc. [4]). Combining tCS with behavioural interventions, such as cognitive bias modification, does not appear to lead to promising results for alcohol use disorder. This might be due to several factors, such as the motivation of the participants (some were not treatment seeking, and therefore might not be motivated to reduce their drinking), or the study design (perhaps there were too few sessions to induce changes). Interestingly, combining tACS with attentional bias modification decreased attentional biases, as well as improving decision-making and decreasing craving in patients with tobacco use disorder. Although this was a proof of concept study [14], it nevertheless demonstrated the potential pertinence of combining these two interventions in SRADs.

Furthermore, a series of limitations of the reviewed studies should be taken into account. Firstly, patient characteristics such as age and sex knowingly influence tCS-induced effects [44-47] but were not always properly considered. In addition, the pattern of substance use disorders is different in men and women. For example, most studies included samples with a majority of men or even men-only. It would be important to include more women in studies. Importantly, it would be imperative to determine whether there are differences between sexes in tCS responses. Secondly, the majority of studies included detoxified and abstinent patients, while

other stages of SRADs (e.g., sated, non-treatment seekers) remain unexplored. A recent study in non-treatment-seeking tobacco smokers suggested that sated patients responded better to tCS as compared to deprived patients, as reflected by a greater deactivation of the default mode network [29]. To support, acute nicotine in sated, as compared to abstinent, patients may present greater neural plasticity [48], thus presumably they may respond more to tCS. Thirdly, most studies did not include patients with comorbid disorders other than tobacco use disorder. Considering that comorbidities (e.g., mood disorders) are common in SRADs [49], it might be worth examining different subgroups. Fourthly, the motivation to change, which is associated with better response to tCS, remains unexplored [50]. Improving selective attention might be one way to improve motivation [32]. Also, greater motivation may relate to a better adherence to tCS regimens, which likely require several sessions in order to produce clinically meaningful improvements of symptoms [36]. Fifthly, behavioural states before stimulation and individual differences in brain morphometry on the effect of tCS treatments should be considered [51]. For instance, we previously observed that behaviours and brain morphometry impacted tDCS changes on neural substrates in patients with gambling disorder. In one study, there were positive correlations between tCS-induced changes of neurotransmitter levels in prefrontal and striatal regions and gambling related behaviours (i.e., craving, impulsivity, risk-taking) in patients with gambling disorder [52]. In another study, there were positive correlations between tDCS-induced elevations of prefrontal GABA levels and morphometry (volume and thickness) of the DLPFC in patients with gambling disorder [51]. In addition, the use of more objective and standardized outcome measures (e.g., a cue-provoked paradigm for craving) would allow more direct comparisons across studies. Lastly, future work could assess whether tCS can modulate other cognitive functions that may be relevant to SRADs, such as memory bias [53] and mindfulness [54].

4. Conclusion

In conclusion, tCS holds a strong clinical potential to improve cognitive functions when targeting the DLPFC. Further work is needed to determine the most effective

protocols. One interesting therapeutic avenue might be individualized treatments based on patient characteristics such as brain morphometry, age and sex. Future studies could aim to optimize outcomes by combining tCS with medications or behavioural interventions (e.g., cognitive behavioural therapy) in order to improve outcomes even more [36].

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